1. Summary

Hypertension represents a significant global public health problem and economic burden. The progressive nature of the disease from asymptomatic status to end-organ failure contributes to cardiovascular morbidity and mortality as it is responsible about systolic and diastolic heart failure and renal impairment. Despite achievements in pharmacological therapies to provide effective blood pressure control, still considerable percentage of patients are lacking of blood pressure control due to multiple factors. The novel approach of selective renal denervation may be considered as an important tool for treatment of resistant hypertension. In our study, we evaluated, by using transthoracic two- dimensional, doppler and strain rate echocardiography, whether renal denervation has ability to reverse cardiac remodeling processes followed hypertension in patients with refractory hypertension and hence a positive effect on systolic and diastolic dysfunctions. Beside lowering peripheral blood pressure and resting heart rate, we found that renal sympathectomy significantly reduces left ventricular mass and volumes. It facilitates the reverse remodeling that accompanied by improvement of left ventricular diastolic and systolic functions markedly evidenced in the responder's population and particularly those who had evidence of diastolic dysfunction at baseline. Left atrial volume, which was evidenced to be a surrogate marker for the risk of atrial fibrillation development, (Wachtell et al., 2005 b) also significantly reduced after renal denervation independable from blood pressure response. However; left ventricular filling pressure did not exhibit the expected significant changes in our study which recommends coincidental assessment with invasive manoeuvre and long period of follow-up.

Results derived from strain rate imaging supports that left ventricular systolic impairment is in part related to an increased left ventricular mass in patients with hypertension. It is proved that the improvement in echocadiographic parameters as well as left ventricular mass, in parallel with blood pressure reduction after renal denervation, contributed to the improvement of longitudinal left ventricular systolic function and relaxation and stiffness of the left ventricule. These results highlight the function of subendocardium which might play a role in the pathology of diastolic dysfunction. Accordingly, our data support strain rate imaging as a sensitive tool for detection of subclinical phases of left ventricular

dysfunction. It goes deeper insight in the analysis of left ventricular systolic and diastolic functions than do conventional echocardiography and tissue doppler imaging. It might therefore improve the clinical management of patients with heart failure with preserved ejection fraction. The further role of strain rate imaging in clinical practice has to be studied in more details in larger trials.

We conclude that in addition to blood pressure lowering effect, the selective denervation of the renal sympathetic nerves reverses cardiac remodeling and improves both systolic and diastolic functions in patients with refractory hypertension. These data suggest a cardiovascular prognostic benefit of renal denervation in patients with refractory hypertension. After reviewing drug trials, (Devereux et al., 2004 and Pierdomenico et al., 2010) we recommend investigation of the cardiovascular prognostic benefit of renal denervation in further big trials.

2. Zusammenfassung

Wir konnten durch Verwendung transthorakaler Echokardiographie inclusive strain rate imaging zeigen, dass die renale sympathische Denervation in Patienten mit therapierefraktärer arterieller Hypertonie neben Blutdruck und Herzfrequenz auch die linksventrikuläre Masse und das linksventrikuläre Volumen reduziert sowie das linksventrikuläre Remodelling verbessert.

Weiter verbessert die renale Denervation die systolische und diastolische linksventrikuläre Funktion in denjenigen Patienten, die mir einer Blutdrucksenkung reagierten und im Besonderen in denjenign mit diastolischer Dysfunktion bei Studieneinschluss. Wie erwartet war die Verbesserung stärker in den Patienten, die die Zielblutdruckwerte erreichten.

Linksventrikuläre Füllungsdrücke zeigten keine signifikante Veränderung in unserer Studie was auf die Überlegenheit invasiver Messungen und langer Nachbeobachtung hindeutet.

Der in unserer Studie dargestellte Effekt der renalen Denervation auf die myokardiale Struktur und Funktion suggeriert einen kardioprotektiven Effekt der renalen Denervation in Patienten mit therapierefraktärer arterieller Hypertonie.

Wir fanden das strain rate imaging eine sensitive Technik zur Identifizierung subklinischer Phasen der linksventrikulären Dysfunktion. In unserer Studie wurde es angewandt um die frühen Veränderungen der linksventrikulären systolischen und diastolischen Funktion kurz nach renaler Denervation zu verstehen. strain rate imaging und mitral annular plane systolic excursion waren in der Frühphase nach Therapie sensitiver als konventionelle Echoparameter zur Bestimmung der linksventrikulären systolischen Funktion. Die strain rate imaging Bestimmung deutete darauf hin, dass die systolische Funktionseinschränkung ist mit einer gesteigerten linkventrikulären Masse in Patienten mit arterieller Hypertonie assoziiert und zeigte dass die Verbesserung echokardiographischer funktioneller Parameter wie auch des Massenindices parallel zur Blutdruckreduktion zur Verbesserung der systolischen Funktion sowie der linksventrikulären Relaxation und Steifigkeit beiträgt, die in Patienten mit adäquater Blutdruckreduktion und diastolischer Dysfunktion vor Studienbeginn beobachtet wurde.

strain rate imaging unterstrich zudem die Funktion des Subendokards, das ebenfalls eine Rolle in der Pathophysiology der diastolischen Dysfunktion spielen könnte.

strain rate imaging als neuartige echokardiographische Methode, gibt einen fundierten Einblick in die Analyse der linksventrikulären systolischen und diastolischen Dysfunktion als die konventionelle Echokardiographie und Gewebedoppler-Echokardiographie. Es könnte daher die klinische Betreuung von Patienten mit diastolischer Herzinsuffizienz verbessern. Die weitere Rolle von strain rate imaging in der klinischen Praxis muss im Detail in größeren Studien untersucht werden.

3. Introduction

3.1. Essential hypertension

3.1.1. Size of the problem and cardiovascular risk

Essential hypertension (HTN), or primary high blood pressure, is a common disorder mostly asymptomatic where systemic blood pressure (BP) remains abnormally elevated for a sustained period of time (Chobanian et al., 2003). HTN is a significant growing global health problem affecting approximately 1.2 billion people worldwide (WHO 2002). One in three adults is affected by high BP and the number of patients with newly discovered hypertension is projected to rise even more (Kearney et al., 2005). Projections show that by 2030, an additional 27 million people could have hypertension, a 9.9% increase in prevalence from 2010 (Heidenreich et al., 2011). HTN remains a leading cause of premature death, responsible for 12.8% of total deaths worldwide, (WHO 2009) being a main cause of stroke, congestive heart failure and kidney disease. About 62% of cerebrovascular and 49% of ischemic heart disease patients are attributed to suboptimal blood pressure control. Following diabetes, HTN is the second most common cause of end-stage renal failure and 80% of chronic kidney disease patients develop HTN at some point in the course of their disease (WHO 2002). From 1998 to 2008, the death rate caused by HTN increased 20.2%, and the actual number of deaths rose 49.7% (Centers for Disease Control and Prevention. 2011). The risk of cardiovascular mortality is related linearly with both systolic and diastolic pressures, doubling for every 20-mm Hg and 10-mm Hg increase in the systolic and diastolic blood pressure, respectively, above 115/75 mm Hg (Roger et al., 2012). The prevalence of hypertension increases with age, obesity and sedentary lifestyles (Whelton et al., 2002). Since all three factors are growing worldwide, HTN treatment represents a huge and growing clinical challenge as well as a major public health cost burden. The estimated annual global healthcare expenditure directly attributable to hypertension is estimated by $500 billion (Lawes et al., 2008). On the other hand, World Health Organization report has classified HTN as a risk factor for cardiovascular diseases and one of the most important preventable causes of premature

morbidity and mortality in developed as well as developing countries (WHO 2002 and Ezzati et al., 2002).

For actual detection of the size of the problem, European Society of Cardiology, European Society of Hypertension and the United States Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, have established guidelines for blood pressure classification (see **Table 1**). (Chobanian et al., 2003).

Classification	**Systolic (mmHg)**	**Diastolic (mmHg)**
Normal	90–119	60–79
Prehypertension	120–139	80–89
HTN:		
Stage 1	140−159	90–99
Stage 2	≥160	≥100

Table 1: Blood pressure classification (Chobanian et al., 2003)

(Note that target blood pressure for diabetics is <130/80)

3.1.2. Blood pressure regulating mechanisms

BP is controlled by a complex processes in the body through the interaction of electrical, mechanical and hormonal influences. The sympathetic nervous system (SNS) is the main component of blood pressure control as it connects the brain, heart, blood vessels and kidneys, each of which plays a vital role in the regulation of the body's BP. The brain mainly plays an important role, processing and sending signals to the rest of the SNS. The heart plays an important mechanical role by adjusting the heart rate and the force of cardiac contractility to regulate BP. The blood vessels themselves also play a mechanical

role, influencing BP by either dilating to lower blood pressure or constricting to raise BP. The final and perhaps the most central contributors to the regulation of BP are the kidneys. They play electrical, mechanical and hormonal roles to regulate systemic blood pressure. The kidneys regulate BP by signaling the need for increased or lowered pressure through the SNS (electrical), by controlling the amount of fluid in the body (mechanical) and by releasing hormones that influence the response of the heart and blood vessels (hormonal) (Kearney et al., 2005).

3.1.3. Essential hypertension as a consequence of chronic elevated central and renal sympathetic tone

A network of afferent and efferent sensory, chemo- and baroreceptor nerve fibers, lie in the adventitia of the renal artery allover the kidney (Vonend et al., 2003). This net work terminates in the blood vessels, the juxtaglomerular apparatus and the renal tubules (Barajas et al., 1992). It connects with hypothalamus providing an integration of the renal artery with the brain stem (DiBona 2005). This signaling pathway is responsible for altering the peripheral arterial resistance, the venous capacitance vasculature, peripheral and central chemoreceptors, and sympathetic activity of the kidney (Schlaich et al., 2004). Activation of renal sensory afferent nerve is caused by various stimuli such as renal ischemia, hypoxia, and oxidative stress as well as intrinsic renal diseases (DiBona 2005). Following these stimuli, the sensory afferent signaling reaches the posterior hypothalamus, directly influences central sympathetic outflow, throughout the entirety of the sympathetic system including kidneys (Esler 2010). Accordingly, activation of the sympathetic nerve fibers that innervate all organs involved in the direct control of peripheral vascular resistance, management of central and peripheral chemo-receptors, directly affect cardic contractility, vascular tone, heart rate and rhythm, management of total body salt and water through both renal mechanisms and control of intravascular circulating blood volume in the splanchnic vessels and of course the kidney itself (DiBona 2005). The consequences of incease central sympathetic drive responsible for many diseases linked to hypertension and systolic heart failure, such as insulin resistance,

sleep disorders, diuretic resistance and congestion (Fitzgerald 2009). Therefore, it is well established that the renal blood flow and renal sympathetic nerve activity are very important in the regulation of renal function and fundamental to the control of blood pressure (Barrett et al., 2001) and there is considerable evidence that activation of the SNS plays an important role in the pathogenesis of several cardiovascular diseases, including HTN (Lohmeier 2001).

It has been investigated that essential hypertension is largely neurogenic, both initiated and sustained by SNS over-activity proved using radiotracer dilution methodology measuring spillover of noradrenaline from the kidney (Esler 2000).

Thus, reduction of excessive central sympathetic activity, following the selective removal of renal signals to the hypothalamus, is therapeutically attractive in the treatment of disorders commonly linked by sympathetic over-activity (Doumas et al., 2010).

3.2. Hypertensive heart disease

Chronically elevated systemic blood pressure and sustained increased workload on the heart leads to a series of pathological changes (remodeling processes) and begin as a compensatory mechanism to minimize wall stress. They mainly take place in the left ventricle (LV) in the form of hypertrophy and remodeling (Bauml et al., 2010). Pathological changes involve myocardial fibrosis, ischemia, cardiomyocyte impairment, apoptosis, endothelial dysfunction and increased arterial stiffness. All these abnormalities together often lead into a vicious circle which determine the phenotype form of hypertensive heart disease (Hellenic 2008).

One of the key components in the development of hypertensive heart disease is the myocardial fibrosis (Yamamoto et al., 2002). It is mainly accused to promote diastolic dysfunction (DD) resulting in the increase of LV filling pressure. These changes compromise cardiac function after a series of poorly characterized events (transition to failure), in which the left ventricle dilates and the LV ejection fraction (EF) (systolic function) progressively declines (Drazner 2005) **Figure (1).**

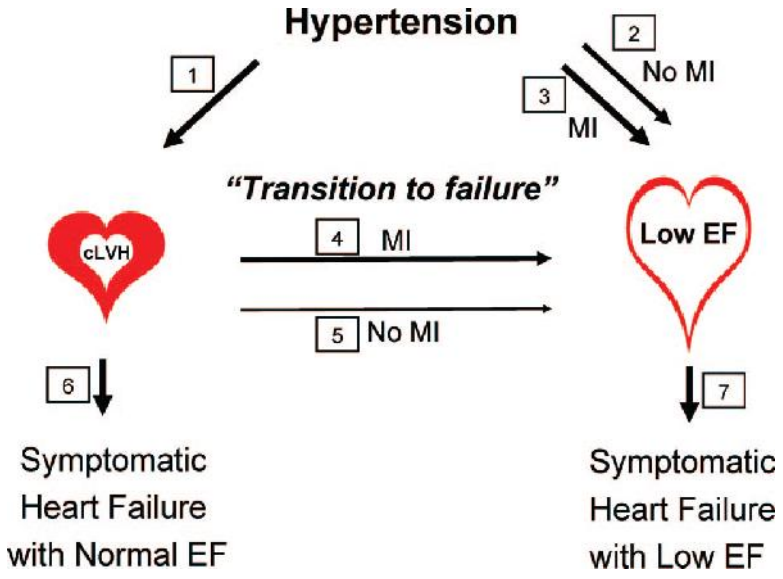


Figure (1): Hypertension and transition to failure. MI; myocardial infarction, cLVH; concentric left ventricular hypertrophy, EF; ejection fraction. (Drazner 2005).

Clinically hypertensive heart disease covers a broad spectrum ranging from asymptomatic LV remodeling (either a concentric or an eccentric pattern) to overt heart failure (with either a preserved or a reduced left ventricular ejection fraction) (Drazner 2011).

3.2.1. LV remodeling and myocardial hypertrophy

The combination of volume and pressure overloads causes LV geometric adaptations. This LV adaptation ranges from concentric remodeling and concentric left ventricular hypertrophy (LVH) up to heart failure (transition to failure, see before) (Hellenic 2008). The influences of neurohormones beside response to the mechanical stress from elevated BP are considered the mechanisms responsible about progression from LV hypertrophy to failure (Hill et al., 2008, Diez et al., 2010). The most commonly response of the myocardium from the longstanding pumping against an elevated after load is LVH. LVH is defined as an abnormal increase in the mass of the left ventricular myocardium caused by a chronically increased workload on the heart (Lorell et al., 2000). The development of LVH is highly correlated with systolic hypertension. In the Framingham Heart Study,

even borderline isolated systolic hypertension at an elderly age was associated with increased left ventricular wall thickness and impaired diastolic filling (Sagie et al., 1993). There is considerable inter individual variation in the progression from HTN to the increase in LV mass and the changes in geometric pattern (ventricular dilatation or wall thickening) (Drazner 2011).

3.2.1.1. Echocardiographic diagnosis of LVH

The diagnosis of LVH is important because it is an indicator of end-organ damage in arterial hypertension. The risk of cardiovascular morbidity and mortality is two-to-four-fold increased in LVH patients compared to patients with normal left ventricular mass as LVH may facilitate many cardiac complications of HTN, including congestive heart failure, ventricular arrhythmias, myocardial ischemia and sudden death (Casale et al., 1986). On the other hand, treatment-induced regression of LVH decreases adverse cardiovascular events and improves overall survival; therefore treatment of LVH should be considered as well as BP control in hypertensive patients (Okin et al., 2004).

It is well established that echocardiography is the test of choice to assess LVH. It is much more sensitive than electrocardiography (Devereux et al., 1986). Left ventricular mass index (LVMI) is considered the most valid parameter to define LVH. The left ventricular wall thickness alone is not a good indicator of LVH and does not accurately assess the presence of LVH (Leibowitz et al., 2007). Accordingly, wall thickness should not be used alone to define this pathology, as often happens in clinical practice. Echocardiography can measure end-diastolic diameter (EDD), posterior wall thickness (PW), and interventricular septum thickness (IVS) **Figure (2).** From these measurements and the patient's height and weight, LVMI can be calculated (Lang et al., 2005). By echocardiography, we can also detect other associated structural and functional abnormalities.

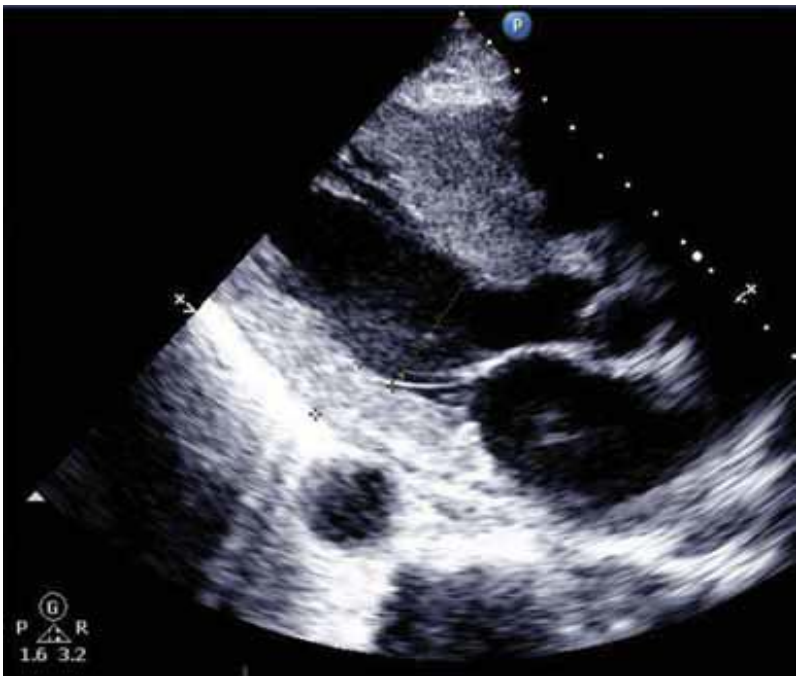


Figure (2): Left ventricular hypertrophy. It is diagnosed by an elevated left ventricular mass index, which is calculated from the intraventricular septal thickness (IVSd), posterior wall thickness (PWTd), and left ventricular end-diastolic internal diameter (LVIDd) (Devereux et al., 1986).

3.2.2. Left atrial remodeling in HTN

A time-dependent adaptive regulation processes against external stressors is established to maintain homeostasis, these adaptive processes are referred to as LA remodeling (Nattel 1999). In HTN, volume/pressure overload and diastolic dysfunction represents the main stressors (Colucci et al., 2005). The LA remodeling mechanisms depend on the strength and the duration of exposure to these "stressors" and they are reversible in the earlier and midterm stages of LA structural and functional disturbances (Everett et al., 2000 and Kumagai et al., 2003) and usually irreversible over the longer term (Li et al., 1999). These include myocyte growth, hypertrophy, necrosis, and apoptosis; alterations in the composition of extracellular matrix; recalibration of energy production and expenditure; changes in the expression of cellular ionic channels and atrial hormones (Colucci et al., 2005). These maladaptive processes which lead to LA remodeling

resulted in structural, functional, electrical, metabolic, and neurohormonal consequences (Casaclang-Verzosa G et al., 2008).

3.2.2.1. Consequences of LA remodeling in HTN

Ultrastructural changes in hypertension- induced remodeling are marked by extensive interstitial fibrosis and myocyte hypertrophy (Khan et al., 2004) which provides circuits for re-entry (Shi et al., 2001) making the LA more vulnerable to atrial fibrillation (AF) development. Whereas atrial dilatation is the hallmark of structural remodeling, atrial arrhythmias, especially AF, are the most common manifestations of LA electrical remodeling (Schoonderwoerd et al., 2005). In hypertensive patients, who present with an enlarged left atrium, have a 42% increased risk of developing atrial fibrillation (Krahn et al., 1995), cardiovascular morbidity e.g. heart failure (Bayes-Genis et al., 2007) , stroke (Douglas et al., 2003) and sudden cardiac death (Wachtell et al., 2005 a and Alsaileek et al., 2006).

3.2.2.2. Echocardiographic assessment of LA structural remodeling

In sinus rhythm, left atrial volume has a high sensitivity and specificity as a measurement of diastolic dysfunction and LV filling pressures (Tsang et al., 2002). Echocardiographic assessment of left atrial volume indexed to body surface area (LAVI) was proposed as a marker of both diastolic LV dysfunction and cardiovascular risk and may improve the process of cardiovascular risk stratification (Alsaileek et al., 2006). It is required also to support the diagnosis of heart failure with normal ejection fraction which can complicate uncontrolled longstanding HTN (Yoshida et al., 2009).

3.2.3. Neurohormonal disturbances associate LA and LV remodeling with HTN

Increases in atrial natriuretic peptide (ANP) (Dietz et al., 2005), brain natriuretic peptide (BNP) (Tsioufis et al., 2006), angiotensin II (Ang-II), aldosterone, transforming growth factor beta-1(Hanna et al., 2004), and sympathetic hyperinnervation (Tsioufis et al.,

2006) have been described in association with the remodeling process. Atrial natriuretic peptide is a direct vasodilator, which lowers systemic blood pressure and inhibits renin and endothelin secretion, myocyte hypertrophy, and fibroblast collagen synthesis (Miyauchi et al., 2003). Mechanical stretching of the LA is the strongest stimulus for ANP secretion, which is augmented by endothelin and inhibited by nitric oxide (Franco et al., 2004). Cardiac BNP is another marker for LA and LV remodeling in response to an increase of atrial or ventricular diastolic stretch and their secretion results in natriuresis, vasodilation, and improved LV relaxation (Lim et al., 2006 and Barclay et al., 2006). In the case of LA remodeling, BNP is significantly correlated with indexed LA volume in patients with diastolic heart failure (Lim et al., 2006), stable chronic heart failure (Barclay et al., 2006), hypertension (Inoue et al., 2000), In contrast to its usefulness in symptomatic isolated diastolic LV dysfunction, natriuretic peptides were a suboptimal screening test for preclinical diastolic LV dysfunction (Boldt et al., 2004).

3.2.4. Diastolic dysfunction in hypertensive heart

The function of the heart can be classified into (1) pumping function during the systolic phase, impairment of which can lead to low cardiac output, which has usually been evaluated by the presence of low EF and (2) filling function, during diastolic phase, and it's impairment results from decrease the LV compliance and relaxation with increase of the LV stiffness and that can lead to congestion (Mandinov et al., 2000). Ventricular relaxation is a dynamic active process leading to flow of blood from the left atrium (LA) into the LV across a pressure gradient (Ommen et al., 2000). Changes in diastolic compliance and relaxation are direct consequences of exceeded tissue stiffness (Mandinov et al., 2000). There is growing evidences that myocardial stiffening depends mainly upon myocardial fibrosis rather than LV wall thickening and myocyte hypertrophy in hypertensive heart (Yamamoto et al., 2002). Therefore, diastolic dysfunction (functional impairment) can be also presented in hypertensive patients with normal LV mass. (Aeschbacher et al., 2001).

EF may be normal in the presence of diastolic dysfunction in a phenomena referred as ‘heart failure with normal EF (HFNEF)’ or ‘heart failure with preserved EF (HFPEF)’ (Yu et al., 2002 and Paulus et al., 2007).

3.2.4.1. Problem of heart failure with preserved ejection fraction (HFPEF)

The prevalence of cases presented HFPEF increased from 38 to 54% of all heart failure cases over the last two decades. The prevalence of HFPEF in the heart failure population rises by about 1% a year especially among elderly, female gender, diabetics obesity population, arterial hypertension, and LVH (Owan et al., 2006). Symptoms due to HFPEF, as in systolic heart failure, are attributed to low cardiac output and pulmonary congestion. As the increase in LV filling pressure is the direct cause of pulmonary congestion, assessment of LV filling pressure has been becomes a main clinical concern, not only in systolic heart failure but also in DHF (Yu et al., 2002 and Baicu et al., 2005). Morbidity, hospitalization rates, and healthcare costs per patient are very similar between systolic and diastolic heart failure (Bursi et al., 2006). Moreover, no great difference in mortality between both forms of heart failure was found (Bhatia et al., 2006 and Bursi et al., 2006).

3.3. Echocardiographic assessment of diastolic function in hypertensive patients

Echocardiography can indirectly assess myocardial relaxation, LV stiffness, and filling pressures to predict the hemodynamic performance of LV during diastole. Doppler study is primarily applied to evaluate hemodynamic and the diastolic function. Study of morphologic and functional properties of the heart which correlates with diastolic dysfunction is recommended during the Doppler echocardiographic assessment and important to establish the diagnosis of diastolic dysfunction in certain difficult situations and as well as for the definition of HFPEF. These properties involve LVH, LA volume and function and pulmonary artery systolic and diastolic pressures (Nagueh et al., 2009).

3.3.1. Blood flow Doppler assessment of LV diastolic function

Pulsed wave Doppler is mainly used to identify Isovolumetric LV relaxation time (IVRT), ratio of peak early (E) to peak atrial (A) Doppler mitral valve flow velocity, deceleration time (DT) of early Doppler mitral valve flow velocity, (see methods) and ratio of pulmonary vein systolic (S) and diastolic (D) flow velocities were originally considered to be indicative of diastolic LV dysfunction and allow classification of the grade of DD if they exceeded specific cut-off values indexed for age groups (Nagueh et al., 2009). The combined use of these variables provided a semi quantitative estimate of LV end-diastolic pressure is also supported by observations in hypertensive patients (Rusconi et al., 2001).

3.3.2. Assessment of LV diastolic function using Tissue Doppler Imaging (TDI)

TDI measures myocardial motion (measured as tissue velocity) relative to the transducer with high spatial (mm) and temporal resolution. Tissue velocity indicates the rate at which a particular point in the myocardium moves toward or away from the transducer. In this setting TD derived velocity is obtained via pulsed Doppler (PW) (by placing a sample volume at a particular location). Measurements can be obtained at the septal and at the lateral side of the mitral annulus (Ommen et al., 2000). The peak systolic (S) shortening velocity and the early diastolic (E') lengthening velocities are considered to be sensitive measures of LV systolic or diastolic function. E depends on LA pressures, LV relaxation kinetics, and age but E' depends mostly on LV relaxation kinetics and age. Hence, in the ratio E/E', effects of LV relaxation kinetics and age are eliminated and the ratio becomes a measure of left atrial driving pressure or LV filling pressure. E' can also reflect the amount of blood entering the LV during early filling, whereas E represents the gradient necessary to make this blood enter the LV. A high E/E' thus represents a high gradient for a low shift in volume (Rivas-Gotz et al., 2003 and Diwan et al., 2005). Cut off values for the E/E' is established in which when the ratio exceeds 15, LV filling pressures are elevated and when the ratio is lower than 8, LV filling pressures is considered to be low i.e normal. An E/E' ratio ranging from 8 to 15 is suggestive but non

conclusive evidence of diastolic LV dysfunction and needs to be supported with other non-invasive investigations to confirm the diagnosis (Ommen et al., 2000). It is known now that E/E' is superior as predictor of prognosis than clinical or other echocardiographic variables (Hillis et al., 2004). See **Table 2** and **Figure (3)**.

Measurement	Abnormality	Clinical implications
e′	Decreased (<8 cm/s septal, <10 cm/s lateral, or <9 cm/s average)	Delayed LV relaxation
E/e′ ratio[a]	High (>15)	High LV filling pressure
	Low (<8)	Normal LV filling pressure
	Intermediate (8–15)	Grey zone (additional parameters necessary)
Mitral inflow E/A ratio[b]	'Restrictive' (>2)	High LV filling pressure
		Volume overload
	'Impaired relaxation' (<1)	Delayed LV relaxation
		Normal LV filling pressure
	Normal (1–2)	Inconclusive (may be 'pseudonormal')
Mitral inflow during Valsalva manoeuvre	Change of the 'pseudonormal' to the 'impaired relaxation' pattern (with a decrease in E/A ratio ≥0.5)	High LV filling pressure (unmasked through Valsalva)
(A pulm–A mitral) duration	>30 ms	High LV filling pressure

A pulm–A mitral = time difference between pulmonary vein flow A-wave duration and mitral flow A-wave duration; E/A = ratio of early to late diastolic mitral inflow waves; e' early diastolic velocity of mitral annulus; E/e' = ratio of the mitral inflow E wave to the tissue Doppler e' wave; HF heart failure; LV left ventricular. Different cut-off points exist in different consensus documents. (Paulus et al., 2007 and Nagueh et al., 2009). For the cut-off points mentioned in this table both septal and average e' may be used.bHighly variable and unsuitable for diagnosis on its own; largely depending on loading conditions; age-corrected normal values exist (Nagueh et al, 2009).

Table 2: **Common echocardiographic measures of left ventricular diastolic dysfunction in patients with heart failure** (McMurray et al., 2012)**.**

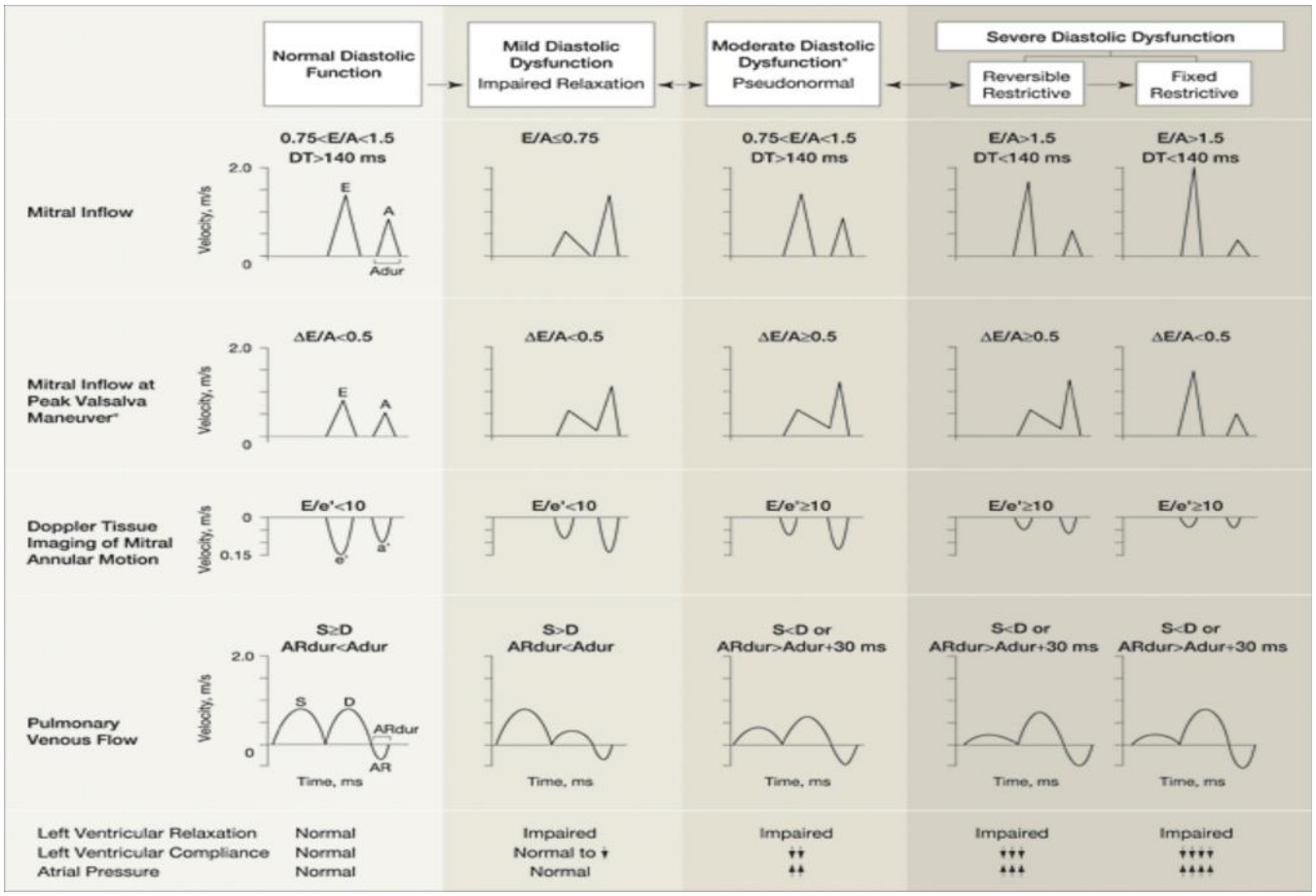


Figure (3): Doppler criteria for classification of diastolic function. E, early mitral valve flow velocity; E´, early TD lengthening velocity; E/A, ratio of early (E) to late (A) mitral valve flow velocity; DT, deceleration time; S, peak systolic shortening velocity; Vp colour M-Mode flow propagation (Redfield et al., 2003).

Doppler echocardiographic technique is used frequently in the daily practice as a tool to provide functional informative data. It is widely available, safe non invasive and inexpensive imaging modality (Nagueh et al., 1997).

3.3.3. Need for newly applied techniques in the assessment of diastolic function

Although hemodynamic data with echocardiography often simply established, it may be valid in a given patient but are not necessarily applicable to all patients. Doppler echocardiographic measurements of diastolic function can show individual variability

and can even vary from day to day in the same patient. the mitral inflow velocity profile is affected by several factors including age, heart rate, volume status, left atrial pressure, and rate of myocardial relaxation, sometime it is restricted in accurately evaluating the diastolic function (Alarm et al., 1992 and Sohn et al., 1997). Also, the diagnosis of diastolic heart failure using the available guidelines is difficult to apply in some cases. Thus the optimum way of treatment is still controversial in such cases as long as the mechanisms of the disease are not completely defined. Simple informative diagnostic tests are needed especially for better identification of the early stages of diastolic dysfunction (Vinereanu et al., 2005). To apply echocardiographic methods for investigating of such problems, it is possible to choose either a general simple approach with high feasibility and reproducibility or a more sophisticated one. Although the former is suited for clinically trials, the latter may be superior for answering mechanistic questions. Recently, deformation measurements by strain analysis appear to have good reproducibility and can be applied to investigate regional deformation and to approach mechanistic problems missed by conventional parameters (Nagueh et al., 2009).

3.4. Strain and strain rate imaging (SRI)

Strain is defined as a quantitative measurement of the amount of movement of an object in response to applied force and it is expressed by %, whereas SR is the rate at which this change or movement occurs and expressed by s-1 (Abraham et al., 2007).

Echocardiographic strain and is a tool for the evaluation of myocardial systolic function and has been found to be superior to velocity analysis by TDI, or conventional ultrasound techniques, for quantification of regional myocardial function. The spectrum of clinical applications is very wide due its ability to differentiate between active and passive movement of myocardial segments and to evaluate components of myocardial function such as longitudinal myocardial shortening that are not visually assessable. The high sensitivity of both TDI-derived and 2D speckle tracking derived strain and strain rate data for the early detection of myocardial dysfunction recommend this new non-invasive diagnostic method for routine clinical use (D'hooge et al., 2002 and Dandel et al., 2009). Systolic strain represents percentage shortening when measurements are done in the long

axis and percentage radial thickening in the short axis. Accordingly, lengthening and thickening strains are assigned positive values and shortening and thinning strains negative values (Dandel et al., 2009). SRI may also provide important quantitative data in the evaluation of diastolic function. The high temporal resolution of strain imaging provides the ability to analyze short-lived mechanical events during diastole (Takemoto et al., 2005). In which regional diastolic strain ratios are related to regional stiffness and can differentiate between stunned and infarcted myocardium (Pellikka et al., 2004). The evidence exists that changes in early diastolic strain rate can predict angiographic disease (Perk et al., 2007).

3.4.1. Speckle-tracking derived two-dimensional (2D)-strain

It is newly emerging technology that measures myocardial deformation (strain) by tracking speckles (acoustic markers) in grayscale echocardiographic images. The motion pattern of myocardial tissue is reflected by the motion pattern of speckles. The speckles function as natural acoustic markers that can be tracked from frame to frame. Later on velocity and strain are obtained by automated measurement of distance between speckles. Special software allows spatial and temporal image processing with the ability to recognize and select these elements on ultrasound images and then automatically calculates strain and strain rate values (Abraham et al., 2007 and Dandel et al., 2009).

The method is angle independent; therefore, measurements can be obtained simultaneously from multiple regions within an image plane. The 2D echocardiographic loops obtained from parasternal and apical views are processed offline. This requires only one cardiac cycle to be acquired but SRI data can be obtained only with high resolution image quality at high frame rate (about 50-70 frames per second (FPS)) (Marwick et al., 2006 and Dandel et al., 2007).

3.4.2. Emerging role of SRI in the evaluation of hypertensive heart disease

3.4.2.1. SRI in the assessment of diastolic function

As mentioned before, Doppler and TDI methods are widely available and easy applied method to identify DD. Although that, the comprehensive understanding of diastolic pathophysiology is still considered as a clinical challenge due to the drawbacks and some times difficulties in applying these parameters (Nagueh et al., 2009). Garcia-Fernandez et al., 1999 proved that despite of normal mitral flow Doppler, still up to 40% of the myocardial segments may have measurable regional diastolic motion abnormalities. In hypertensive patients, SRI technique permits the evaluation of changes of LV diastolic function even if they are free from clinical manifestations of HF (Bruch C, et al., 2002). However, the role of strain and strain rate imaging in defining diastolic dysfunction is still under investigation (Nagueh et al., 2009, Oxborough et al., 2009 and Amundsen et al., 2009).

3.4.2.2. SRI in the assessment of systolic function

TDI was used before to study LV systolic function. The advantage of pulsed-wave TDI is that it does not require high-end equipment, specific software, or offline analysis (Anderson et al., 2008). But it has drawbacks hinder the accuracy of evaluation myocardium mechanics during systole. TDI interrogates motion at a single point in the myocardium with reference to a point outside the chest (the transducer). It is found that it is influenced by translational motion of the chest wall and tethering effects (normal apical segments pull an abnormal basal segment toward the apex). Moreover, single point interrogation (depicting tissue displacement) does not fully capture true myocardial mechanics (D'hooge et al., 2002). Accordingly, it requires sampling of multiple regions from different cardiac cycles, which is time consuming and renders tissue velocity peaks more difficult to identify (Anderson et al., 2008). In contrast, strain rate imaging technology now enables quantitative measurement of regional LV function independent of cardiac rotational motion, chest wall movements and tethering artefacts and thus may

be superior to tissue velocity in depicting regional or global myocardial function (D'hooge et al., 2002). Speckle tracking derived from 2D SRI can also provide an angle-independent imaging for myocardial deformation (Langeland et al., 2004). Impairment in longitudinal myocardial function was reported in different groups of patients despite normal EF and FS (Koyama et al., 2003). This impairment was not observed with TDV (Ballo et al., 2007) but was determined by SRI (Koyama et al., 2003). Systemic Arterial

Hypertension leads to tiny vascular abnormalities beside myocardial fibrosis which mainly harms the endocardium (Martinez et al., 2003). Affection of subendocardial function could be early detected by examining the longitudinal function abnormalities using global longitudinal strain measurement (Wang et al., 2008). Application of SRI using speckle tracking has been used in detecting subclinical myocardial abnormalities resulted from hypertrophy and hypoperfusion in LV hypertrophy, as well as in distinguishing the different causes of LV hypertrophy (Pavlopoulos et al., 2008 and Imbalzano et al., 2011). Accordingly, the application of a 2D speckle tracking is promising and can be widely applied, as a simple clear diagnostic test, in the study of subclinical or overt LV systolic dysfunction and for better understanding of the early stages of diastolic dysfunction (Nagueh et al., 2009) with improved both interobserver and intraobserver variability compared with TDI derived strain. Therefore, more studies are needed to define its clinical value in defining LVH associated subclinical systolic dysfunction (Afonso et al., 2008).

3.5. Mitral annular plane systolic excursion (MAPSE)

3.5.1. Background

The LV wall is composed of both circular (radial) and longitudinal myocardial fibers, in which the later fibers contracting earlier and dominate in subepicardial and subendocardial layers and in the papillary muscles (Timek et al., 2001). It has a complex three-dimensional motion pattern composed of: longitudinal apical motion along the ventricular long axis (base to apex), rotation and sphincter-like motion (Zaky et al.,

1967). The apical displacement represents shortening of the left ventricle along its long axis. Mitral annulus is considered tightly coupled component of the mitral valve/left atrial/left ventricular complex that aids in effective efficient valve closure as well as uncomplicated left ventricular filling (Timek et al., 2001).

3.5.2. Functional importance and clinical application

Cardiac disorders can impair both longitudinal and radial contractile function. However, it has been suggested that in pathologic conditions (e.g., myocardial ischemia or hypertrophy, dilated cardiomyopathy, and hypertrophic cardiomyopathy), long-axis myocardial function is the first to be impaired (Bolognesi et al., 2001). Impairment of Long axis left ventricular contraction and relaxation has attracted interest in recent years as it could help in early diagnosis of cardiac dysfunction. It is easy to be evaluated through measuring of mitral annular plane systolic excursion (MAPSE) by M-mode echocardiography. MAPSE was found to be correlated to LV function calculated by two-dimensional echocardiography, radionuclide ventriculography, as well as contrast cineangiography (Höglund et al., 1989 and Alam et al., 1992 a) which makes it a good indicator of LV systolic function and very sensitive parameter in many different cardiac pathologies (Höglund et al., 1989, Pai et al., 1991 and Florian et al., 2012). Left atrioventricular plane displacement was found to be reduced in AF, most likely due to the absence of atrial contration which contributes to left ventricular diastolic filling (Alam et al., 1992 b). Thus, it is possible that left atrioventricular plane displacement is also affected by left ventricular diastolic performance (Willenheimer et al., 1999). Therefore, MAPSE has been established as a method of measuring left ventricular systolic and diastolic function and as an index of left atrial function (Jones et al., 1991, Pai et al., 1991, Alam et al., 1992 c and Simonson et al., 1998).

3.6. Poor treatment reality

3.6.1. Therapeutic approaches in the management of HTN

Pharmaceutical therapies used in the management of HTN involve multiple agents acting with different mechanisms of action. Centrally acting sympatholytic drugs aim to disrupt the electrical signals involved in the activation of the SNS. Agents designed to lower the mechanical load in the circulatory system, such as diuretics, inhibit sodium and water retention to lower fluid volume. Perhaps most effective, several agents target electrical, mechanical and endocrine activities of the kidneys (see before). These drugs include beta blockers (to reduce enzymes release and heart rate), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) and aldosterone blockers (to counteract rennin angiotensin aldosteron system RAAS) (Chobanian et al., 2003). The aim of antihypertensive therapy should be to reduce the blood pressure as far as possible (Heagerty et al., 2004). A reduction in SBP by 10 mmHg is associated with a reduction in cardiovascular events of up to 25% and these effects are more prominent in stroke than in coronary artery disease (Perkovic et al., 2007). Another potential therapeutic target for the treatment of hypertension is to reverse structural and functional changes result from maladaptive regulatory mechanisms (remodeling process) that is activated to overcome the increase in pressure-volume work load and to minimize wall stress that associate the increase in arterial blood pressure.

It is proved that patients who had a lower left ventricular mass index during treatment with antihypertensive drugs had lower rates of cardiovascular morbidity and all-cause mortality (Okin et al., 2004). Regression of electrocardiographic LVH in hypertensive patients has also been shown to be associated with decrease the incidence of atrial fibrillation (Okin et al., 2006) and hospitalizations for heart failure (Okin et al., 2007).

To treat HTN induce DD, we should look for the treatment of the underlying HTN adequately as a preventable factor and that will contribute to counteract the remodeling process accompanied HTN being the main mechanism for the development of DD (Diez et al., 2002 Yusuf et al., 2003 and Bursi et al., 2006).

The direct impact of reversing LA remodeling on cardiovascular outcomes remains to be seen, but the evidence indirectly suggests significant reduction of risk of AF development as an outcome (Wachtell et al., 2005 b). Still the drugs that modify the renin angiotensin-aldosterone system appear to have particularly powerful effects on LV and LA remodeling processes and their consequence e.g AF development and risk of stroke, beyond their beneficial effects on blood pressure regulation (Tsang et al., 2002, Tsang et al., 2006 and Tanaba et al.; 2009).

3.6.2. Problem of resistant HTN

Despite the availability of numerous effective pharmacologic agents, adequate BP reduction is not achieved in a large number of patients. It is not unusual, as failure to achieve BP control even occurred with proper use of multiple antihypertensive drugs. Several patient and physician related aspects contribute to this problem (Sarafidis et al., 2008). About 50% of patients with HTN remain uncontrolled and approximately 15–20% percent of those are resistant (Lloyd-Jones et al, 2010). Resistant hypertension is defined as blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes including diuretics (Pantelis et al., 2008).

This leaves patients at high risk for major cardiovascular events as long standing uncontrolled HTN is strongly associated with increasing the risk of stroke, heart failure, coronary heart disease, chronic kidney disease diabetes, obstructive sleep apnea and LVH (David et al., 2008 and WHO 2009).

Approximately 45% of ischemic heart disease deaths and 51% of stroke deaths are directly linked to systolic BP (SBP) (WHO 2009). Efforts to overcome resistance to pharmacotherapy have attracted the attention into the role of the sympathetic nervous system in such problems. It plays a critical role in the pathophysiology of HTN and its adverse sequences mainly LVH making it an attractive therapeutic target (Schlaich et al. 2011 a).

3.7. Renal sympathetic denervation (RD)

Certain disease conditions were linked to sympathetic nervous system hyperactivity. this cluster of diseases includes hypertension (Esler et al., 1988), heart failure (Triposkiadis et al., 2009), sleep disturbances (Narkiewicz et al., 1998), metabolic syndrome and glycemic control (Mancia et al., 2007), and chronic kidney disease (Hausberg et al., 2002). the risk of deaths among heart failure patients is associated with sympathetic nervous system hyperactivity (Triposkiadis et al., 2009). Salt and water retention in some forms of heart failure may be mediated by renal sympathetic activity and selective renal denervation may in part used for the treatment or prevention of heart failure and the cardiorenal syndrome (Sobotka et al., 2011). Elevated sympathetic activity of the renal efferent nerves in hypertension mediated by promoting sodium retention, decreasing renal blood flow and glomerular filtration, and increasing renin release, which known as activation of the renin-angiotensin-aldosterone neurohormonal cascade (DiBona et al., 2010). Similarly, hypothalamic signaling activates renal somatic afferent nerve activity, which may mediate effects indirectly related to systemic hypertension (Kandzari et al., 2012). The mechanistic relationship between renal nerve activation and high blood pressure was recognized and investigated since long time to find therapeutic opportunities related to selective renal sympathectomy in patients with refractory hypertension (DiBona et al., 2010). Surgical attempts to attenuate sympathetic drive in attempt to reduce BP have been applied as early as the 1920s in severely hypertensive patients. Although severe side effects developed after the procedure, improvements in BP control and survival were demonstrated in treated patients, highlighting the effectiveness of this old concept (Smithwick et al., 1953). Recently, efforts have led to the emergence of a novel catheter-based approach using radiofrequency (RF) energy for selectively ablation and disruption of the renal nerves. This new technique provides safe and durable blood pressure reduction and that offers hope of successful therapy for the group of hypertensive patients unresponding, unwilling or unable to take maximal doses of multiple anti hypertensive therapy (Kandzari et al., 2012).

Analysis of initial pilot studies (SYMPLICITY HTN-1 First-in-Human and additional phase I studies), showed sustained reduction in office-based systolic and diastolic blood

pressures from baseline measurements through 2 years. A reduction in systolic blood pressure of at least 10 mmHg was achieved in 92% of patients (Krum et al., 2009). Preliminary results of patients with uncontrolled hypertension of the open-label randomized SYMPLICITY HTN-2 trial in Europe and Australia represented a 84% of patients treated with sympathetic denervation experienced a systolic blood pressure reduction exceeding 10 mm Hg, and more than 80% had an office blood pressure <160 mm Hg after 6 months. No recorded procedural complications were observed, and renal imaging at 6 months did not identify any renal abnormalities directly caused by denervation or requiring therapy which consider RD as a safe and efficient for the treatment of resistant HTN (Symplicity HTN-2 Investigators 2010).

SYMPLICITY HTN-3 takes place now in 90 research sites allover the United States. It is a prospective, randomized single-blind trial in which 530 patients will be randomized (316 treatment and 158 control). It is designed to evaluate and define the safety and effectiveness of catheter-based bilateral renal denervation for the treatment of uncontrolled hypertension despite taking at least 3 antihypertensive medications of different classes involving diuretice. The primary end point is detected by the change in office-based systolic blood pressure (SBP) from baseline to 6 months and a major secondary effectiveness analysis is the change in average 24-hour SBP by ambulatory blood pressure monitoring from baseline to 6 months (Kandzari et al., 2012). The results of the SYMPLICITY HTN-3 pivotal trial will be submitted to the US Food and Drug Administration for approval of catheter-based renal denervation as a treatment option for resistant hypertension (Kandzari et al., 2012). In addition, it is found that renal sympathetic denervation may have a multiple benifits beyond those directly related to high blood pressure. Recent reports detected that patients with insulin resistance or type II diabetes mellitus, polycystic ovary syndrome, and hypertension have also improved glucose metabolism insulin sensitivity and good glycemic control with renal sympathectomy (Mahfoud et al., 2011 and Schlaich et al., 2011 b) which may therefore provide protection in patients with resistant HTN and metabolic disorders at high cardiovascular risk (Mahfoud et al., 2011).

As discussed, (see before), HTN results in structural alterations which are associated with functional impairment of the LV, i.e., abnormal diastolic function promoting an increased in diastolic filling pressures. Although it was proved that RD is effective and safe therapy for resistant HTN, still the impact of RD on structural modulations and functional impairment is unclear. Theoretically, as long as increased sympathetic drive is believed to contribute to LVH, the reduction of sympathetic outflow following RD is supposed to facilitate the regression of LV remodeling and its consequences (Tsang et al., 2002). If proved true in prospective studies, this therapy may have unique value suggests a prognostic cardioprotective benefit of RD in patients with refractory hypertension.

4. Aim of the study

Using transthoracic 2 D echocardiography, Doppler and SRI, we studied the effect of the RD, as a newly applied therapeutic tool for treatment of resistant HTN, on structural modulations of the heart and functional impairment of LV secondary to HTN. We also studied SRI parameters as new quantitative indices of intrinsic cardiac deformation to answer the question whether or not SRI provides more information from analysing systolic and diastolic functions of the heart than do the conventional echocardiographic parameters.

5. Patients and Methods

5.1. Patient population

All patients were given a written informed consent for invasive procedures. The research protocol was approved by the local institutional Ethics Committee (Nr. 67/11).

68 patients received RD were enrolled based on having an elevated office systolic BP (160 ≥ mm Hg) despite taking ≥3 types of antihypertensive drugs, including a diuretics, at target or maximal tolerated dose. Patients were excluded if they had an estimated glomerular filtration rate (eGFR) of ≤45 mL/min per 1.73 m^2 (according to MDRD formula), a known secondary cause of HTN or chronic kidney disease. Patients with significant renovascular abnormalities and hemodynamically significant renal artery stenosis were also excluded. Renovascluar pathology was assessed by angiography, magnetic resonance angiography, computed tomography angiography, or duplex ultrasound. Patients had to be ≥18 years of age. Patients were investigated before (baseline) and 6 months following renal sympathetic denervation. All the patients underwent complete history and physical examination, assessment of vital signs, review of medications and blood and renal chemistry. The high, weight, heart rate, systolic and diastolic blood pressures were measured at the baseline and at follow-up visits. Body surface area (BSA) and body mass index (BMI) were calculated. For assessment of BP, 24-h BP recordings in addition to office BP measurements at the hospital before enrolment and at the follow-up visits were performed.

5.2. Renal sympathetic denervation procedure

After confi rmation of eligibility, we introduced the treatment catheter (Symplicity by Ardian Inc, Palo Alto, CA, USA and Medtronic, Inc., Mountain View, CA) into each renal artery via femoral access. We applied discrete, RF ablations lasting up to 2 min each and of 8 watts or less to obtain up to six ablations separated both longitudinally and rotationally within each renal artery. During ablation, the catheter system monitored tip temperature and impedance, altering RF energy delivery in response to a predetermined algorithm.

5.3. Echocardiography

Conventional echocardiographic examinations were performed using a Vivid E9 digital ultrasound system (General Electric VingMed Ultrasound, Horten, Norway) with a 3.0 MHz transducer. All echocardiographic studies were performed by experienced echocardiographers. The patients were studied in the left lateral recumbent position. The observer obtained images, together with a simultaneous ECG signal, along the parasternal long and short axes and from the apical 4-, 2-chamber and long-axis views. All recordings included at least 3 cardiac cycles and were digitally stored for off-line analysis. Echocardiographic techniques and calculations of different cardiac dimensions and diastolic function evaluation were performed in accordance with the recommendations of The American Society of Echocardiography Committee (Nagueh et al., 2009). One examining physician performed >80% of the procedures, ensuring high reproducibility. Speckle-tracking derived two-dimensional (2D)-strain was done offline by one investigator. The patients received echocardiographic investigation before and 6 months after RD.

5.3.1. Determination of 2D echocardiographic parameters

Examinations included measurements of cardiac dimensions, including the interventricular septal thickness (IVS), the LV end-diastolic dimension (EDD), the LV end-systolic dimension (ESD) and the LV posterior wall thickness (PW) as measured by M-mode echocardiography at the chordae tendineae level the LV (Lang et al., 2005).
EF was estimated by calculating LV ejection fraction (EF) using the biplane method of discs (modified Simpson's rule), which is the currently recommended method, as follow:
Ejection fraction = (EDV-ESV)/EDV. In which (EDV): end-diastolic volume and (ESV): end-systolic volume (Lang et al., 2005). See **Figure (4).**

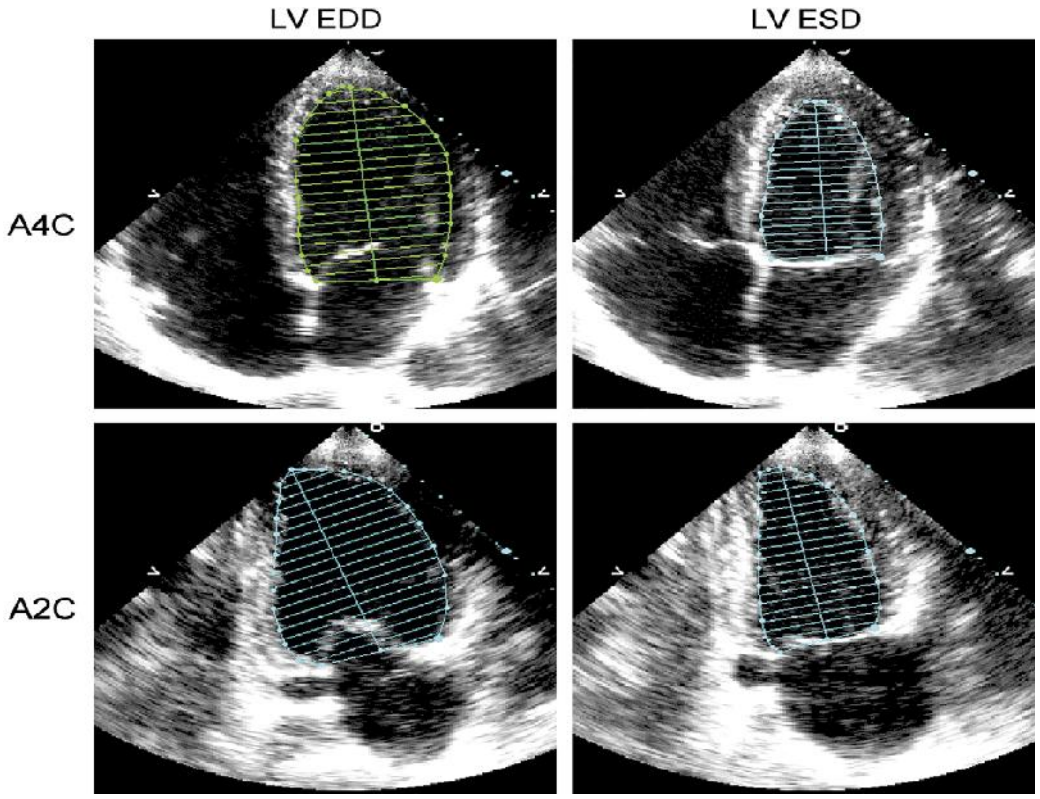


Figure (4): 2-D measurements for volume calculations of left ventricle using the biplane method of discs (modified Simpson's rule), in the apical four-chamber (A4C) and apical two-chamber (A2C) views at end diastole (LV EDD) and at end-systole (LVESD). The papillary muscles should be excluded from the cavity in the tracing (Lang et al., 2005).

Left ventricular mass was determined by the following formula from the recommendations of the American Society of Echocardiography (Lang et al., 2005).

LV mass = 0.8 × {1.04[(LVIDd + PW + IVS)3 – $(LVIDd)^3$]} + 0.6, where LVIDd, PW, and IVS are LV end-diastolic dimension, posterior wall thickness at end diastole, and septal wall thickness at end diastole, respectively. Left ventricular mass index (LVMI) were taken as LV mass divided by body surface area. Cutoff values for the left ventricular mass index have been proposed; as follows: values of > 95 g/m2 in women and > 116 g/m2 in men to define LVH (Okin et al., 2004 and Lang et al., 2005).

Similarly, LA volume indexed calculated from the following formula:

LA Vol / (0.007184* $Length^{0.725}$*$Weight^{0.425}$) (Lang et al., 2005).

LA volume evaluated by biplane method of disks (modified Simpson's rule) by using apical 4-champer and apical 2-champer views at ventricular end systole (maximum LA size) (Lang et al., 2005). See **Figure (5).**

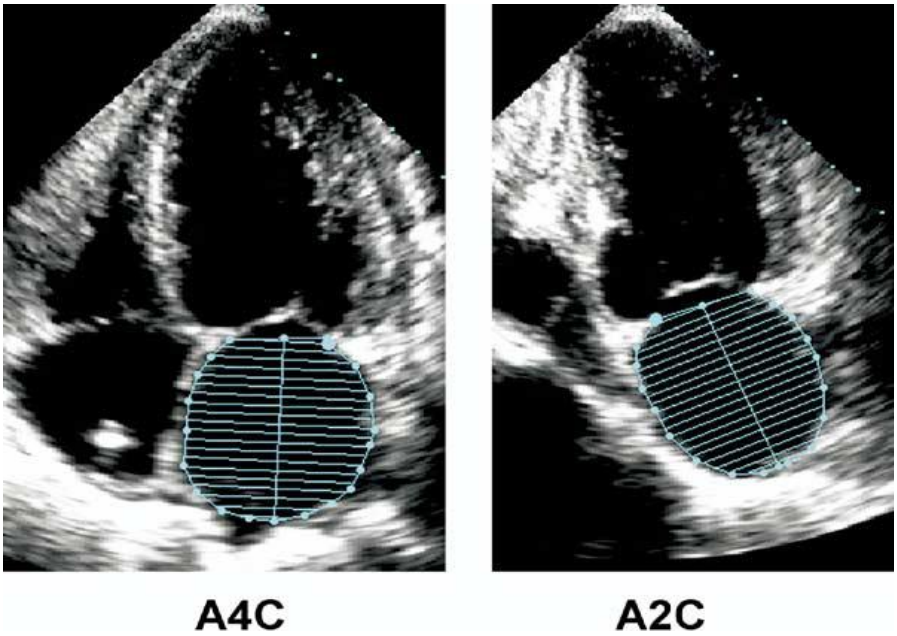


Figure (5): Measurement of left atrial volume from biplane method of disks (modified Simpson's rule) usingapical 4-chamber (*A4C*) and apical 2-chamber (*A2C*) views at ventricular end systole (maximum LA size) (Lang et al., 2005).

5.3.2. Mitral annular plane systolic excursion (MAPSE)

MAPSE was measured by using the apical 4-chamber view focused on the left ventricle. An M-mode vector was placed through the mitral annulus close to the septal and the lateral wall, respectively. The vector was adjusted to be as parallel to the walls as possible by using anatomical M-mode where necessary. MAPSE was measured in millimetres and values of both walls were averaged (Höglund et al., 1988). See **Figure (6).**

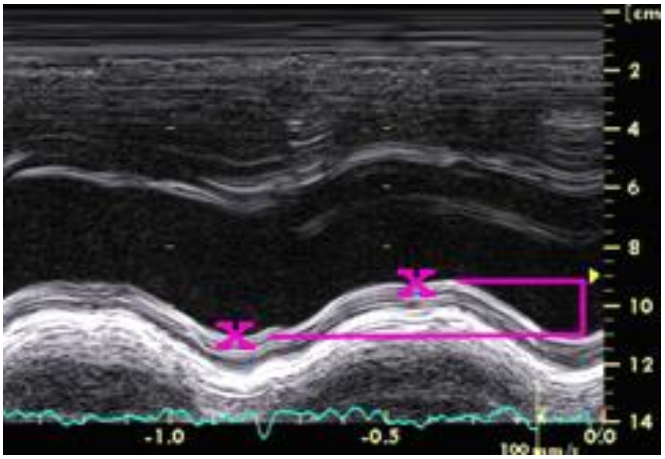


Figure (6): Mitral annulus systolic velocity is assessed with M-mode in apical four-chamber view, placing the examination beam on the lateral mitral annulus (Pai et al., 1991).

5.3.3. Pulsed wave (PW) Doppler and Tissue Doppler imaging (TDI)

Conventional echocardiographic studies were performed using "standard" diastolic parameters. Pulsed-wave Doppler measurements of LV inflow velocity (mitral inflow measurements) in which the sample volume was placed at the tip of the mitral leaflets in the apical 4-chamber view. The following Doppler indices were measured: peak early (E), peak late (A) flow velocities, E/A ratio, deceleration time (DT) **Figure (7)**. Mitral annular velocities were also recorded from the apical 4-chamber view with the pulse-wave Doppler sample volume, (2 mm in size) placed in the septal and lateral corners of the mitral annulus under tissue Doppler imaging mode. Peak early diastolic (E') and late

diastolic annular velocities (A') were determined and both E/E' and E/E' lat. were calculated **Figure (8).**

The above mentioned parameters were used to assess global diastolic function (Nagueh et al., 2009). Filters were set to exclude high frequency signals, and the Nyquist limit adjusted. Gains were minimized to obtain a clear tissue signal with minimal background noise.

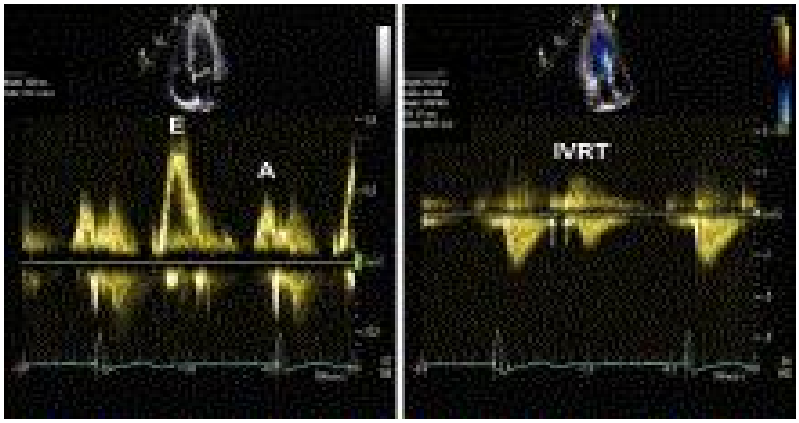


Figure (7): mitral inflow (left panel, from apical 4-champer view) **and isovolumetric relaxation time** (right panel, from apical long axis view) from a normal subject. E, mitral early diastolic velocity; A, mitral late diastolic velocity: IVRT, isovolumetric relaxation time (Wang J et al., 2008).

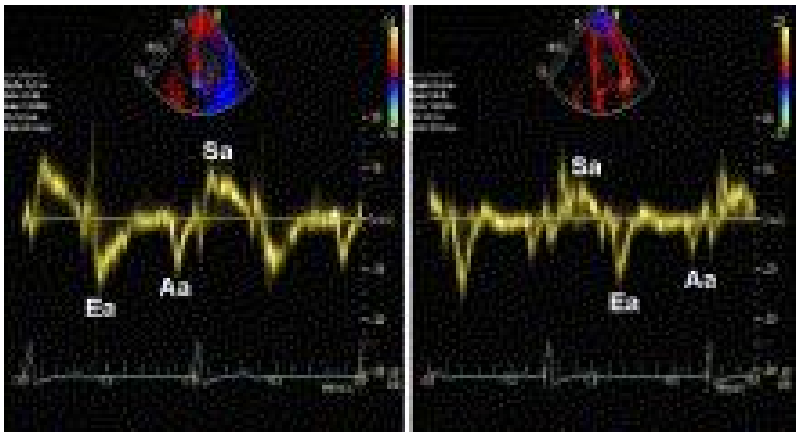


Figure (8): Tissue Doppler at the mitral annulus (TD) signals at the septal side of the mitral annulus from a patient with normal LV diastolic function (left). TD signals of the mitral annulus from the same patient (right). Ea, early diastolic mitral annulus velocity Aa, late diastolic mitral annulus velocity; Sa, systolic velocity during ejection (Wang J et al., 2008).

5.3.4. SRI data Analysis

Myocardial deformation measurements were performed using tissue speckle tracking. Three cardiac cycles were recorded in apical four-, two-chamber, and long-axis views using grey-scale acquisition at a frame rate is between 70 and 90 frames per second. Cardiac cycles were recorded in a cine loop format and stored digitally for subsequent off-line analysis at EchoPAC PC (GE Healthcare, Horton, Norway) workstation for two-dimensional (2D) strain analysis version 110.0.2 (GE Vingmed), averaging three cardiac cycles, which allowing quantitative evaluation of the myocardial function. Offline analysis of apical 4, 2-chamber and long axis views images were completed by tracing the endocardium in end diastole and the thickness of the region of interest adjusted to include the entire myocardium (Moen et al., 2011). Images with frame rates below 40 Hz and above 80 Hz were excluded from analysis to ensure adequate temporal and spatial resolution as well as accurate frame to frame tracking as regards measurement of strain or SRI (strain rate imaging) (Horton et al., 2009).

Strain and strain rate curves were obtained in each of 3 views (4-, 2-chamber and long-axis views) in which all LV myocardial segments (6 segments per view) are presented. Peak strain was defined as the peak negative value on the strain curve during the entire cardiac cycle (Reisner et al., 2004). The average value of peak systolic longitudinal strain and peak systolic strain rate from all three views were then calculated as global systolic longitudinal strain (GS) or (SISYS) **Figure (9) and (10)** and global systolic strain rate (GSR) or (SRSYS), respectively **Figure (11)** (Nagueh et al., 2009).

Similarly, peak global strain rate during early (SRE) and late (SRL) diastole were determined. Diastolic indices E/SRE and SRE/SRL were calculated **Figure (11)** (Wang et al., 2007). The off-line analysis was performed by one investigator.

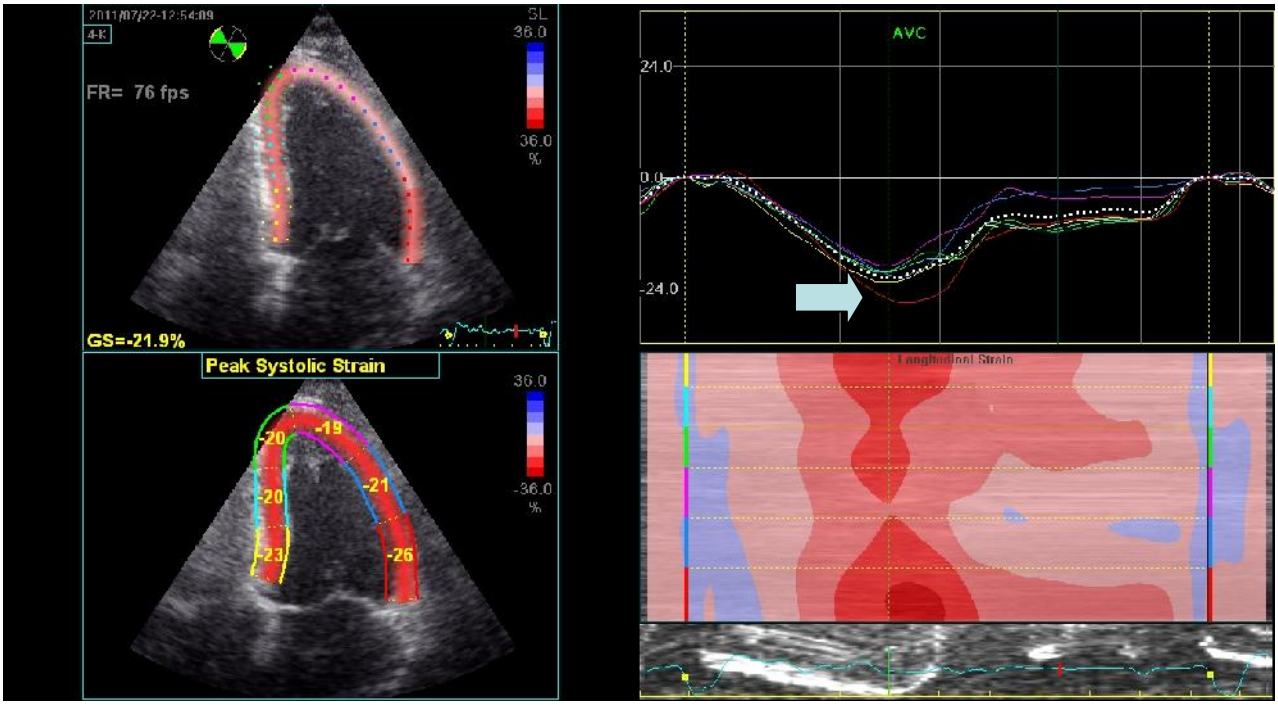


Figure (9): **Systolic longitudinal two-dimensional strain curve** taken from apical 4-champer view. Peak strain (arrow) is the peak negative value on the strain curve during the entire cardiac cycle. Segmental strain curves are presented by continuous lines and the global strain curve by interrupted line.

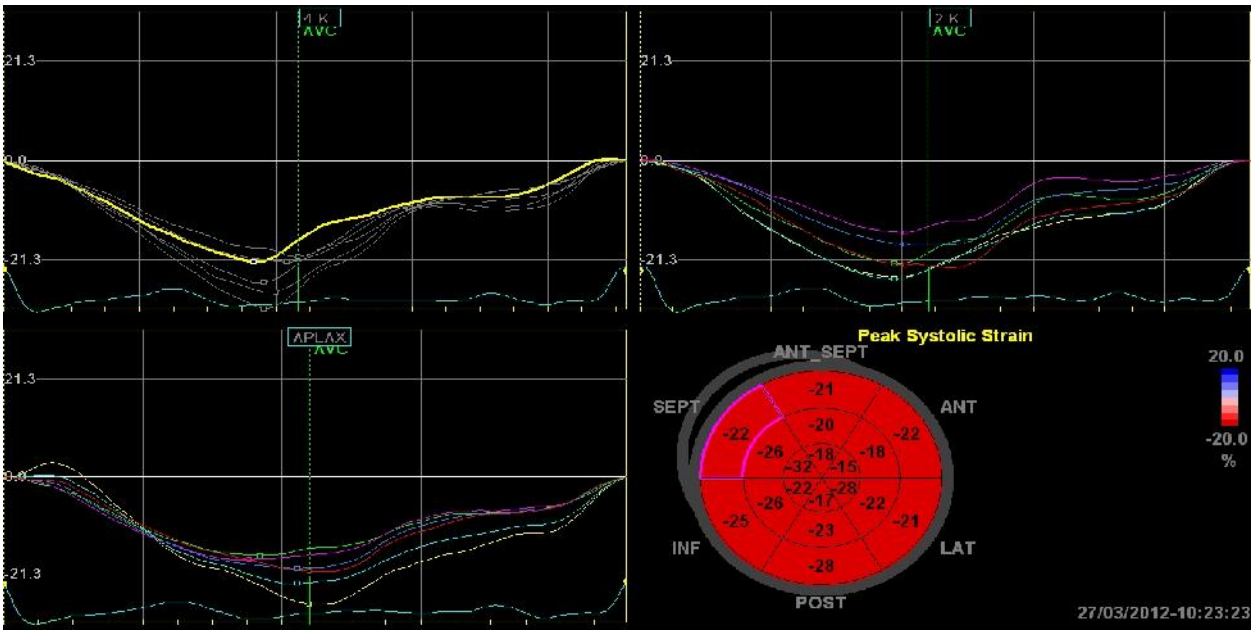


Figure (10): Average value of peak global systolic longitudinal strain from all three views was then calculated as global longitudinal strain (GS).

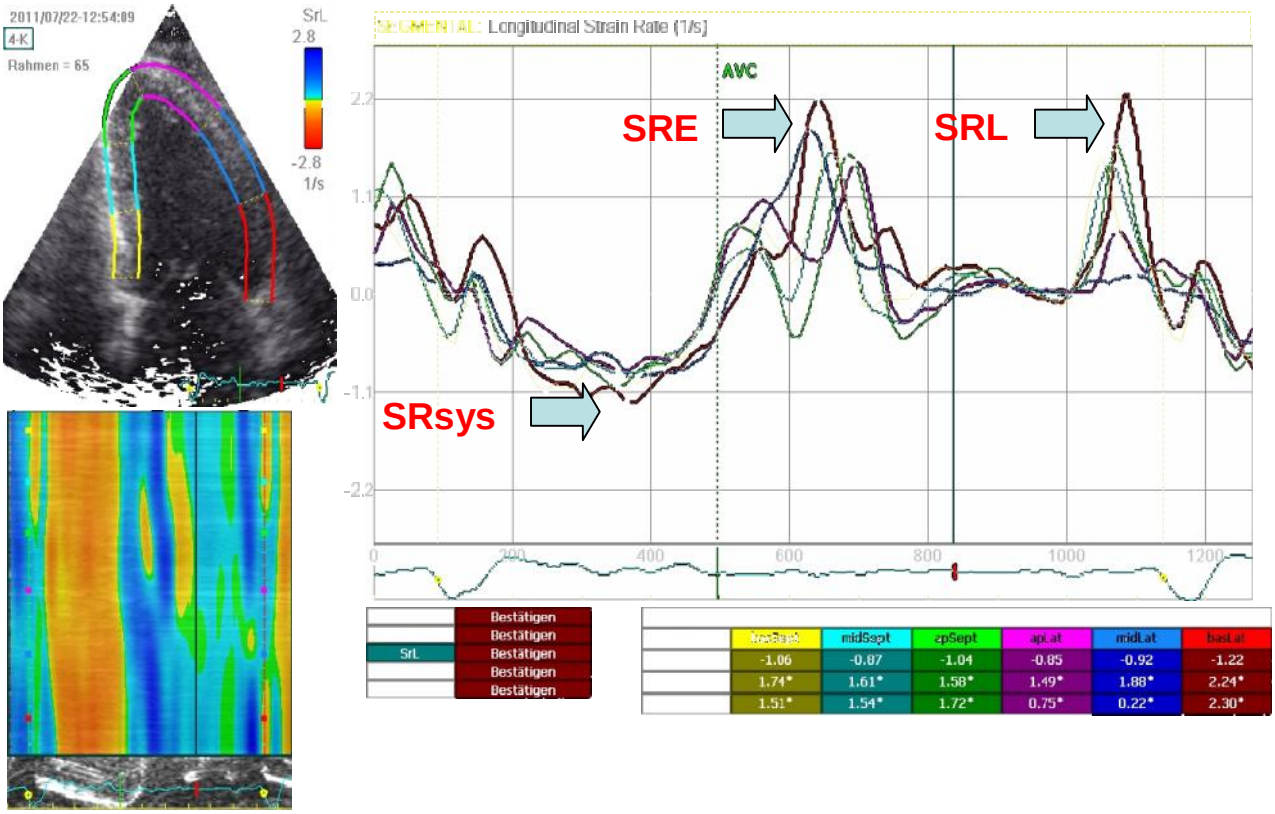


Figure (11): **Longitudinal two-dimensional strain rate curve**. SRE, strain rate during early and SRL, during late diastole; SRSYS, global systolic strain rate; AVC, Aortic valve closure.

Stroke volume (SV) and cardiac output (CO) also calculated to help in assessment of hemodynamic changes in relation to RD as a therapy for resistant HTN.
Both were calculated as follow:

SV= LVOT area * LVOT VTI

CO= HR * SV

In which:

LVOT means left ventricular out flow tract, VTI means velocity time integral and HR means heart rate.

Both LVOT area and LVOT VTI measured with 2D echo (Lewis et al., 1984).

6. Statistics

SPSS Version 20.0 was used for statistical analysis. Results are displayed as mean±SEM. Frequencies are expressed as percentages. Statistical significance of the comparison of measurements at 6 months follow-up and baseline were assessed by a paired Student's *t* test for parametric data and by an unpaired t-test when comparing the differences between subgroups. For categorical data, X^2 analysis was used. Pearson's correlation coefficient (r) was used for analyses of linear correlations.

7. Results

7.1. Patient baseline characteristics

The current study included 68 patients **(Table 3)**, 37 males (54.4 %) and 31 females (45.6 %) with mean age 63.4±1.1 years. The patients group included 12 patients had coronary artery disease, 24 patients had diabetes mellitus (DM) (19 with type 2 DM) and 42 patients hypercholesterolemia. 64 (94%) patients were receiving diuretics; 54 patients (79.4%) were taking ß-blocker, 41 (60.3 %) taking calcium channel blocker, 63 (92.6%) receiving an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or both and 44 (64.7 %) receiving peripheral direct vasodilator, centrally acting sympatholytic agents or both. Body mass index (BMI) and body surface area (BSA) were similar at baseline and at 6 months (BMI 29.4±0.5 kg/m^2 and 2.0 $m^{2,}$ respectively). Baseline and 6 months follow-up were needed for inclusion in the present study. There were no changes in medication during the study period in any of the patients up to the 6-month follow-up.

Table (3) Baseline patient characteristics

Character	Total (n=68)	Responders (n=47)	Non-responders (n=21)	*P* Value *
Age (years)	63.4±1.1	63.0±1.4	64.5±1.8	0.590
Sex (male)	37 (54.4%)	23 (48.9%)	14 (66.7%)	0.175
BMI (Kg/m^2)	29.4±0.5	29.7±0.7	28.7±0.9	0.390
BSA (m^2)	2.4±0.02	2.0±0.03	2.0±0.05	0.786
Diabetes mellitus	24 (35%)	18 (38%)	6 (28.6%)	0.713
Coronary artery disease	12 (18%)	8 (17%)	4 (19%)	0.681
Hypercholesterolemia	42 (62%)	29 (62%)	13 (62%)	0.987
Number of antihypertensive drugs patients receiving, drug class				
ACE inhibitor/ARBs	63 (92%)	43 (91%)	20 (95%)	0.155
Direct rennin Inhibitor	24 (35%)	16 (34%)	8 (38%)	0.764
Beta-blocker	54 (79%)	39 (83%)	15 (71%)	0.276
Calcium-channel blockers	41 (60%)	30 (64%)	11 (52%)	0.373
Diuretics	64 (94%)	45 (96%)	19 (91%)	0.394
Sympatholytics and direct vasodilators	32 (47%)	24 (51%)	8 (38%)	0.560

Values are mean ± SEM or n (%). * For comparison between subgroups, the Pearson chi-square test was performed.BMI: Body mass index, BSA: Body surface area, ACE = Angiotensin-converting enzyme: ARB = angiotensin receptor blocker.

7.2. Effect of RD on hemodynamic

At baseline, overall mean sitting office systolic blood pressure was 173±3 mmHg, and mean sitting office diastolic blood pressure was 92±2 mm Hg, with a heart rate of 68±1 bpm. Renal denervation significantly reduced systolic (-22±3 mmHg; P<0.0001, by 12.5 %) **Figure (12 and 13)** and diastolic (-10±2mmHg; P<0.0001, by 11 %) blood pressures as well as the mean HR (-12±3 bpm; P<0.0001, by 17.6 %) 6 months after the procedure. The patients were divided according to their reduction of BP after RD into responders and non-responders in which the reduction of blood pressure $\geq$ 10 mmHg will be defined as response to RD. Accordingly, 47 patients of the treated patients (69 %) were considered as responders and 21 (31 %) are non-responders. The responders group showed significant reduction in systolic, diastolic BP (-33±3 mmHg and -14±3 mmHg respectively; P<0.0001) and also HR (- 8±3; P<0.0001); however the non-responders sub-group did not show significant reduction in BP after RD but they actually exhibited increase in SBP. On the other hand, HR reduced significantly in this sub group (-21±6; P=0.0004)**.**

A significant difference in the reduction of SBP, DBP and HR was reported between 2 subgroups (P< 0.0001, P=0.01 and P=0.03 respectively) **(Table 4)**. The SV showed increase in all patients but that was statistically non significant. The CO is dependent on HR, so as long as the later decreased significantly, also CO deceased **(Table 4)** and **Figure (14).**

Table (4) Changes in hemodynamic in response to renal denervation

Character	Total (n=68)		Responders (n=47)		Non-responders (n=21)		*P* Value *
	Baseline	**6 month**	**Baseline**	**6 month**	**Baseline**	**6 month**	
SBP (mm Hg)	173.0±3.0	151±3.2**	174.8±3.5	141.9±2.7**	168±5.4	172.3±6.8*	<0.0001
DBP (mm Hg)	92.0±2.3	82.3±1.5**	93.3±2.9	79.8±1.8**	89.0±4.1	88.3±2.8	0.009
Pulse pressure (mmHg)	82.4±2.9	68.7±2.7**	83.5±3.6	62.2±3.9**	75.9±6.2	84.0±6.4*	<0.0001
HR (bpm)	68.3±1.4	60.7±1.2**	67.2±1.1	60.4±1.4**	70.8±2.7	61.2±2.3*	0.027
SV (ml)	85.6±2.2	89.2±2.2	85.6±2.7	88.9±3.9	86.6±4.4	88.8±4.8	0.976
CO (ml/min)	5.7±0.2	5.4±0.2	5.8±0.0	5.4±0.0*	5.9±0.35	5.4±0.4	0.831

Values are mean ± SEM. **P ≤0.001, *P≤0.05 between 6 months and baseline value.
p Value * for difference in **Δ** between responders and non-responders subgroups, the unpaired t-test was performed.
SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, HR = Heart Rate, SV = stroke volume, CO = cardiac output.

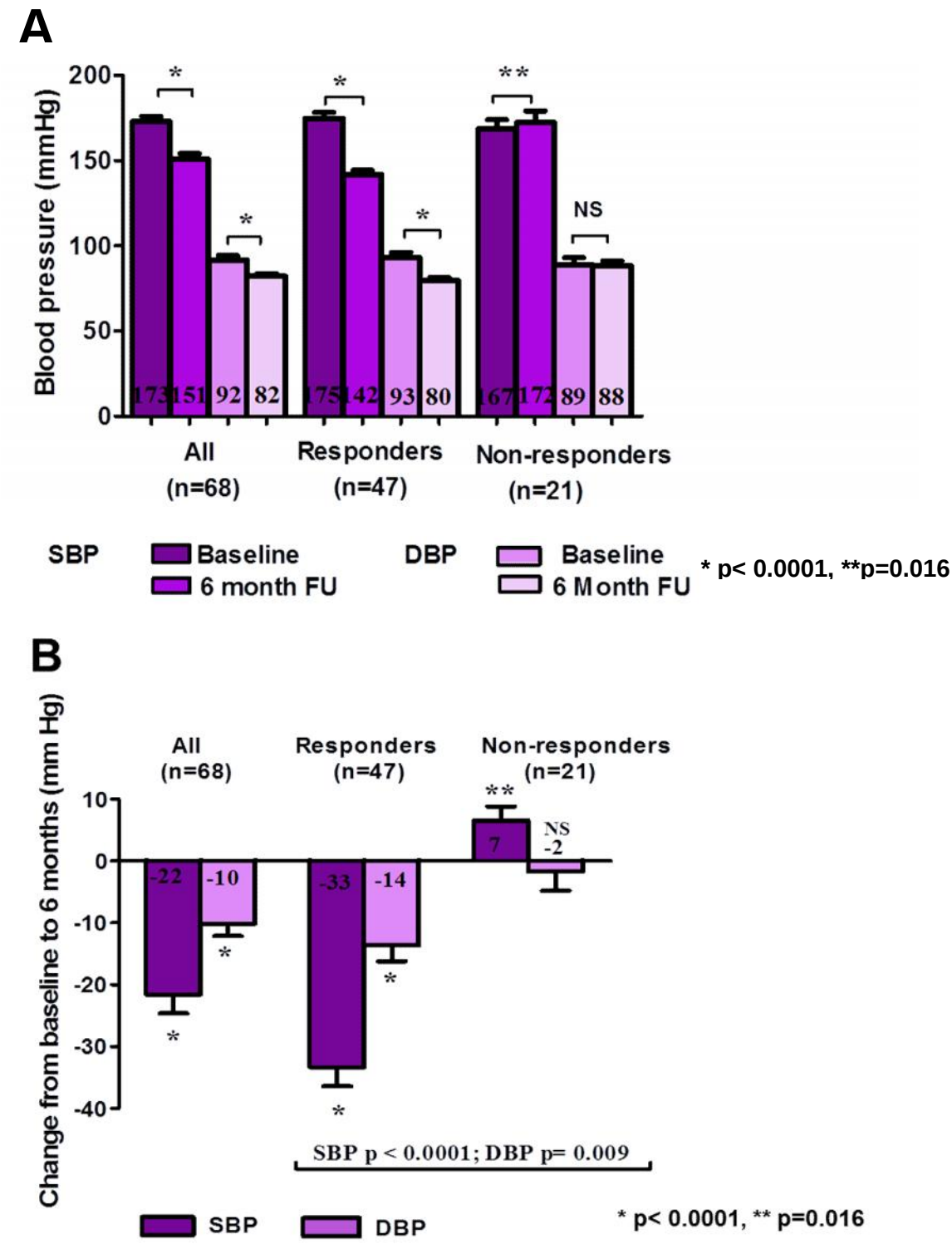


Figure (12): Systolic and diastolic blood pressure (A) and changes in blood pressure (B) 6 months after renal denervation.

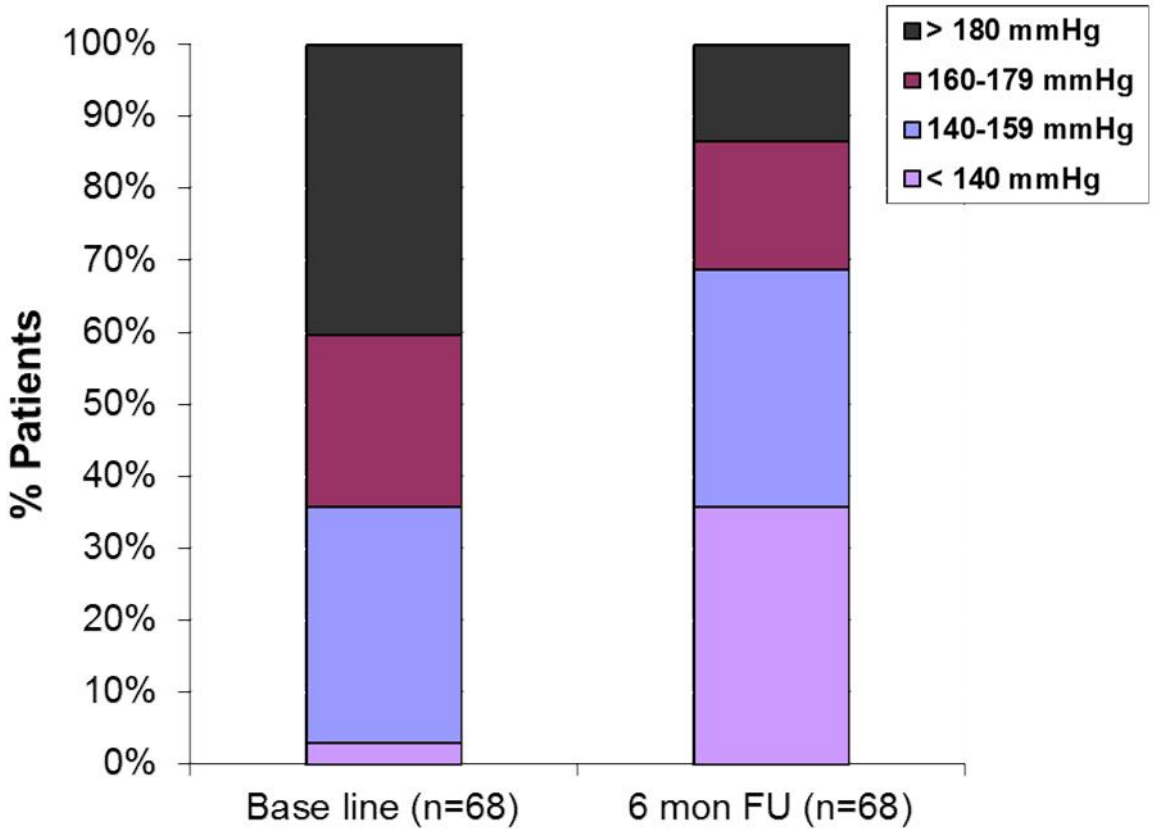


Figure (13): Distribution of systolic blood pressure changes at baseline and at 6 months Follow-up.

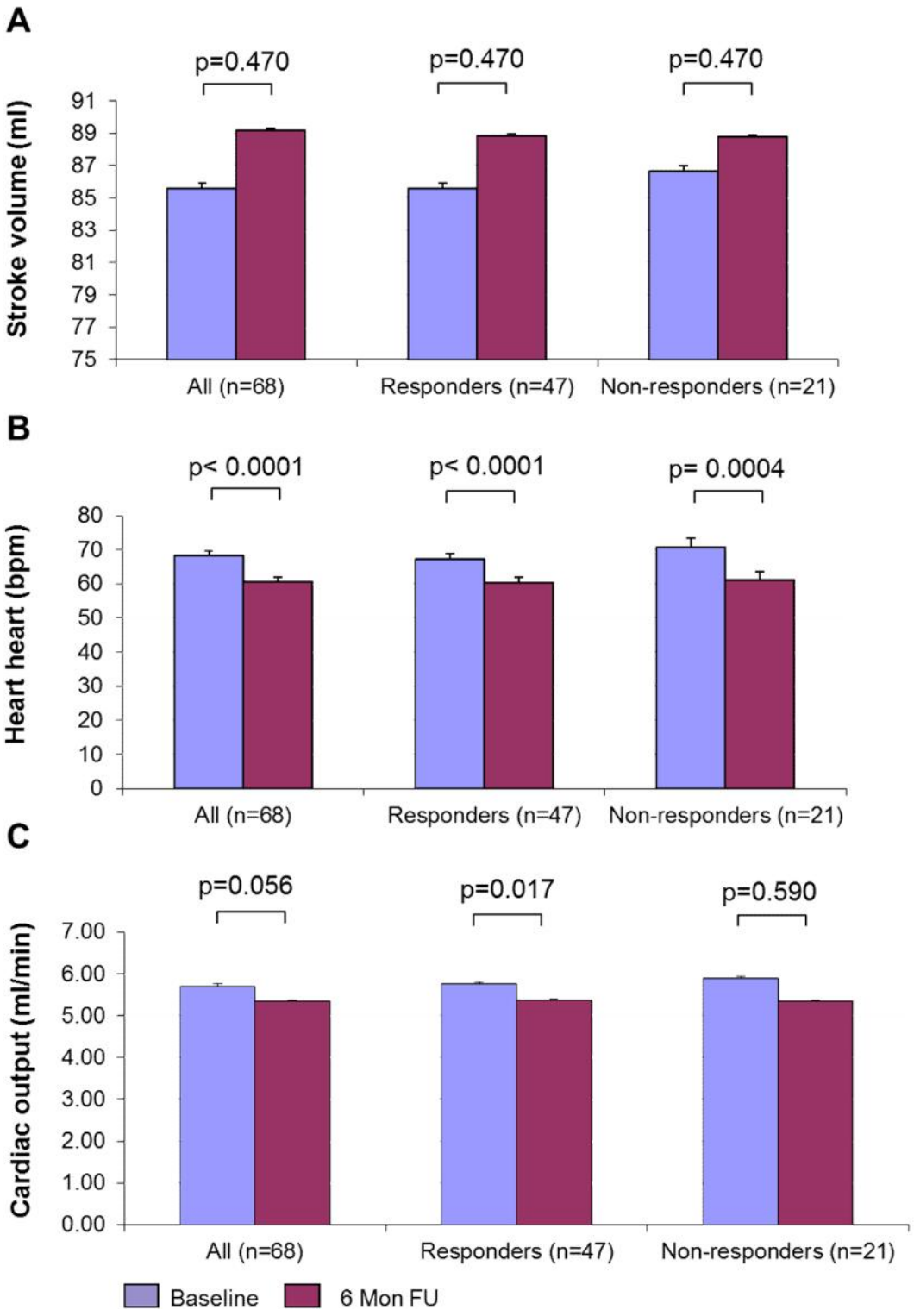


Figure (14): Effect of renal denervation on stroke volume (A), heart rate (B) and cardiac output (C) at rest after 6 months compared with baseline.

7.3. Changes in cardiac structures in response to renal denervation

As shown in **(Table 5)**, the LV mass index reduced significantly in the whole group (-19.37±2.6 gm/m²; *P*<0.0001 by 14.7%). The reduction of LV mass was due to reduction of interventricular septum and posterior wall (-0.65 mm±0.17; *P*=0.0002 and -0.66 mm±0.19; *P*=0.0009 respectively). That is beside the reduction of LV internal diameter in diastole (-2.40±0.43 mm; *P*<0.0001)**.** Furthermore, a 21 % reduction in LV end-diastolic volume (-19.25±3.14 ml; *P*<0.0001) and an 11% reduction in left atrial volume index (-3.77±0.71 ml/m²; *P*<0.0001) was also found. If we look to the subgroups, responders showed regression in LV mass index which was not stronger than in the whole group (-17.00±3.00 gm/m²; *P*<0.0001). That came with a significant reduction in interventricular septum and posterior wall (-0.76 mm±0.20; *P*=0.0005 and-0.48mm±0.22; *P*=0.04 respectively). LV end diastolic diameter also found to be significantly reduced in this subgroup (-2.03±0.50 mm; *P*<0.0001) to contribute to over all reduction in LV mass index. Responders showed a similar reduction in both left atrial volume index (-4.01±0.79 ml/m²; *P*<0.0001) and LV end-diastolic volume (-20.04±4.15 ml; *P*<0.0001). Interestingly, among non-responders the change in left atrial and left ventricular structure was as strong as in the responder group, with significant regression in the mean LV mass index (-24.89±4.89 gm/m²; *P*<0.0001). That was mainly because of the significant reduction in the posterior wall and LV end diastolic parameter (- 0.99 mm±0.37; *P*=0.015 and -3.36 mm±0.81; *P*=0.0005 respectively) without observed significant reduction of the interventricular septum (-0.44 mm±0.30; *P*=0.161). We found less strongly pronounced but still significant reduction in both left atrial volume index and LV end-diastolic volume in this subgroup (-3.35±1.53 ml/m²; *P*=0.041 and -18.35±6.22 ml; *P*=0.008) **Figure (15 and 16)**.

Table (5): Changes in cardiac structures in response to renal denervation

Character	Total (n=68)		Responders (n=47)		Non-responders (n=21)		*P* Value *
	Baseline	6 month	Baseline	6 month	Baseline	6 month	
LVMI (g/m2)	134.9±4.1	115.5±3.2**	131.7±4.4	114.9±3.9**	141.9±8.9	117.0±6.0**	0.144
LVEDD (mm)	52.12±0.6	49.7±0.6**	51.2±0.8	49.2±0.7**	54.2±0.9	50.1±0.9**	0.138
LVESD (mm)	31.7±0.6	30.3±0.5	30.9±0.7	29.8±0.2	33.24±1.2	31.2±1.0	0.239
IVS (mm)	12.8±0.2	12.1±0.2**	12.9±0.3	12.1±0.3**	12.5±0.4	12.0±0.4	0.394
PW (mm)	12.2±0.3	11.5±0.2**	12.2±0.3	11.7±0.2*	12.1±0.4	11.1±0.4*	0.251
LVEDvol (ml)	98.7±3.6	79.4±3.6**	98.3±4.4	78.6±3.2**	99.5±6.4	81.1±6.5*	0.860
LVESvol (ml)	32.0±1.2	27.5±1.1*	30.5±1.2	26.7±3.4*	36.04±2.3	29.3±2.5*	0.167
LAVI (ml/ m2)	34.3±1.03	30.5±0.9**	33.6±1.1	29.6±1.1**	35.8±2.2	32.5±1.2*	0.949
MAPSE (mm)	14.7±0.3	15.4±0.2*	14.8±0.4	15.6±0.3*	14.5±0.6	14.9±0.4	0.487
EF (%)	65.2±0.8	65.43±0.6	65.9±1.0	65.6±0.7	63.4±1.2	65.1±1.3	0.396

Values are mean ± SEM. **P ≤0.001, *P≤0.05 between 6 months and baseline value. *p* Value * for difference in **Δ** between responders and non-responders subgroups, the unpaired t-test was performed.
LVMI = Left Ventricular Mass Index, LVEDD = Left ventricular End Diastolic Dimension, LVESD = Left ventricular End Systolic Dimension, IVS = Interventricular septum Thickness, PW = Posterior Wall Thickness, LVED vol = Left Ventricular End Diastolic Volume, LVESvol= Left Ventricular End Systolic Volume, LAVI = Left Atrial Volume Index, MAPSE = Mitral annular plane systolic excursion, EF= Ejection Fraction.

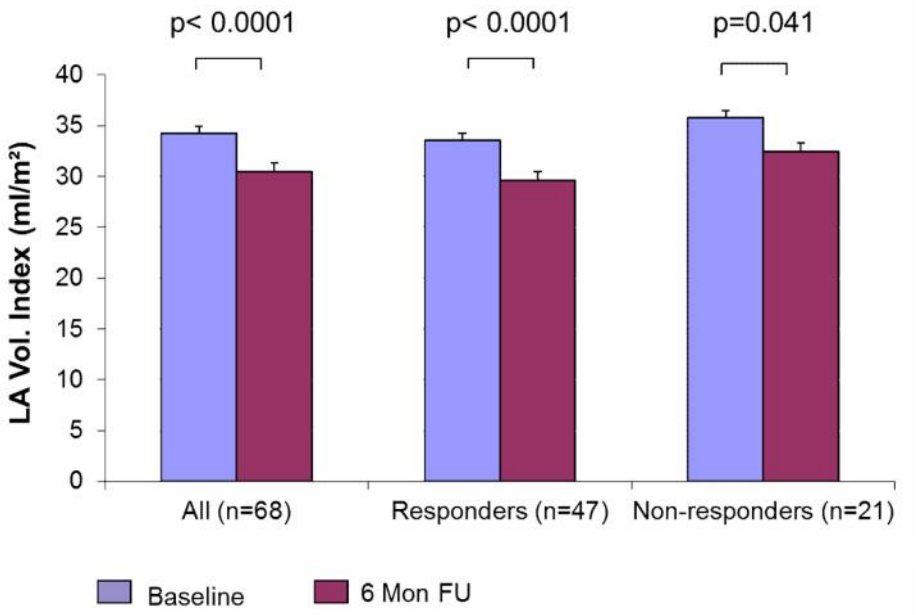


Figure (15): Left atrial volume index decreased 6 months after RD compared with baseline independent from blood pressure response.

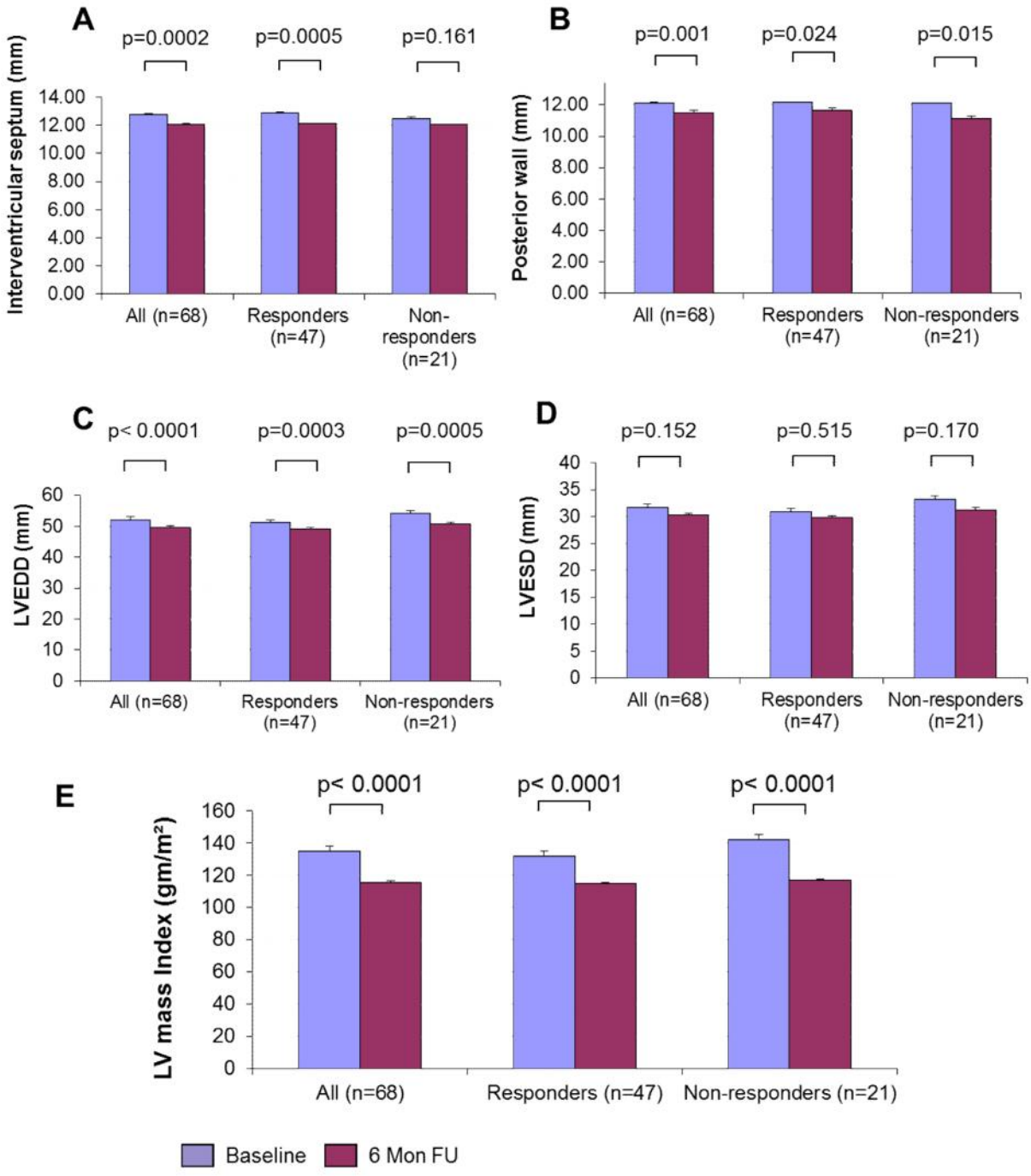


Figure (16): Effect of renal denervation on interventricular septum (A), posterior wall (B), left ventricular end diastolic dimension (LVEDD) (C), left ventricular end systolic dimension (LVESD) (D) and left ventricular mass index (E) after 6 months compared with baseline.

7.4. Changes in systolic function in response to renal denervation

MAPSE, which considered as a longitudinal systolic function parameter, showed a significant increase in the whole group and responders 6 months after RD (0.71±0.26 mm; *P*=0.008 and 0.87±0.30 mm; *P*=0.007 respectively) with no observed significant change in EF. No significant change in MAPSE was observed (-0.45±0.51 ml/m²; *P*=0.388) in non-reponders and also no observed significant change in EF in both subgroups **Figure (17, 24)**.

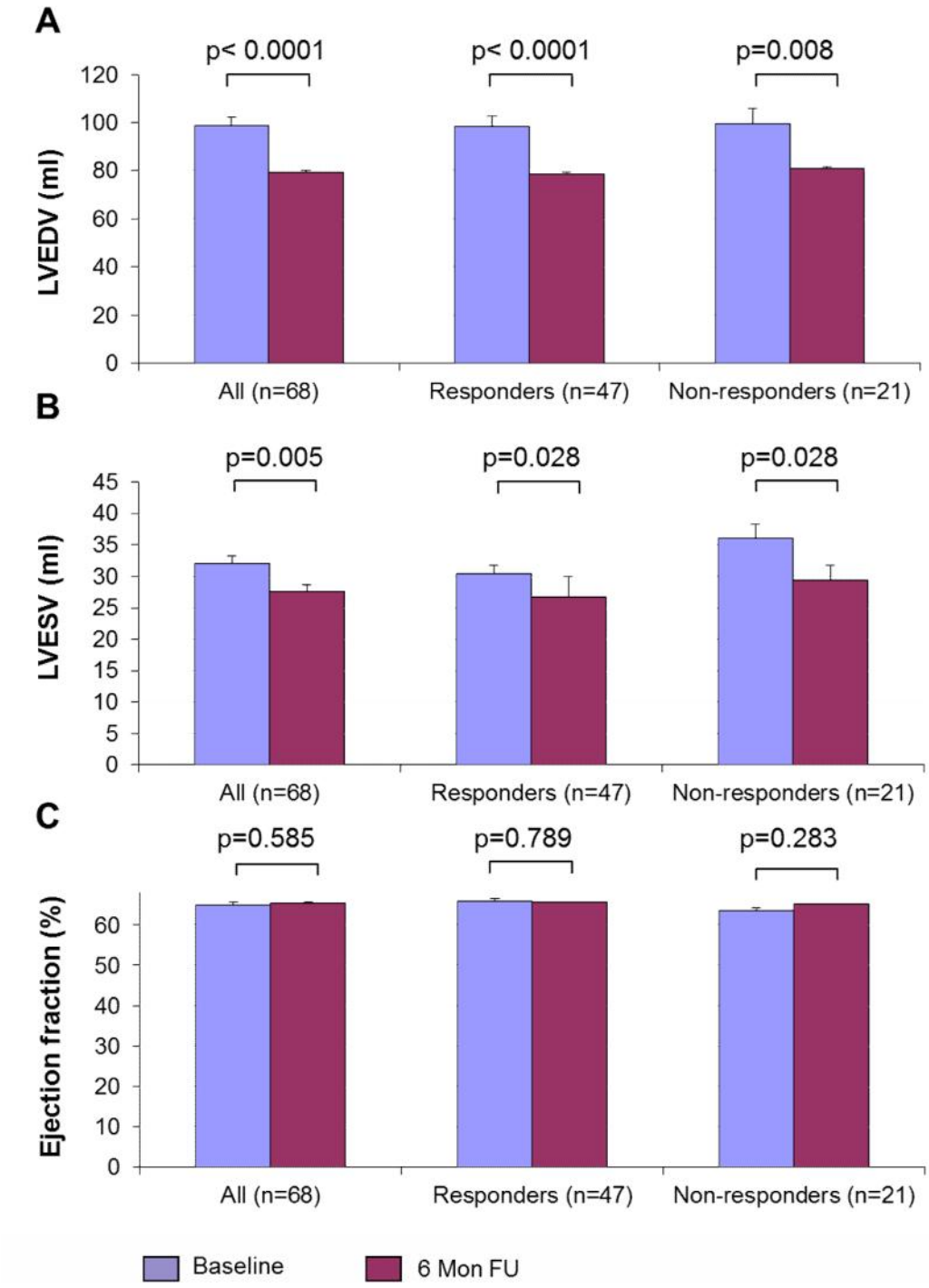


Figure (17): Effect of renal denervation on left ventricular end systolic volume (LVESV) (A), left ventricular end diastolic volume (LVEDV) (B) and ejection fraction (EF) (C) after 6 months compared with baseline. EF: derived from biplane method.

7.5. Changes in diastolic function in response to renal denervation

7.5.1 Blood flow Doppler and TDI assessment of left ventricular dysfunction during diastole

On analyzing LV diastolic function **(Table 6),** the whole group showed significantly increase in E/A ratio after 6 months (0.89±0.04 versus 1.01±0.06; *P*=0.001) with significant shortening in deceleration time (DT) and isovolumetric relaxation time (IVRT) from baseline values (-24.85±8.93 ms; *P*=0.007 and -6.97±2.57 ms; *P*=0.012 respectively). Similarly, the responders showed increased E/A ratio significantly (0.89±0.05 versus 1.00±0.06; *P*=0.013) with significant shortening in DT and IVRT from baseline values (-30.91±10.77ms; *P*=0.006 and -8.55±2.93 ms; *P*=0.006 respectively) after 6 months. Studying the non-responders subgroup, only DT was significantly changed (-30.59±13.57 ms; *P*=0.035) without any observed changes involved E/A ratio or IVRT (0.18±0.09 ms; *P*=0.061 and -1.68±5.14 ms; *P*=0.747 respectively) **Figure (18and 19)**. Concerning the mean values of both E/E' and E/E' lat. ratios, no significant changes were observed compared with baseline values in all patients although significant improvement (increase) in E'sep and E'lat. were reported in whole group as well as responders **Figure (20 and 21).**

Table (6): Changes in diastolic indices derived from conventional and strain rate echocardiography in response to renal denervation

Character	Total (n=68)		Responders (n=47)		Non-responders (n=21)		*P* Value*
	Baseline	**6 months**	**Baseline**	**6 months**	**Baseline**	**6 months**	
Mitral flow							
E max (m/s)	67.7±2.7	73.2±2.1*	67.1±3.4	72.6±2.6	68.5±4.1	74±3.5	0.940
A max (m/s)	80.6±2.4	78.3±2.4	79.6±3.0	76.95±2.8	82.8±3.9	81.2±4.8	0.460
E/A	0.89±0.04	1.01±0.06**	0.89±0.05	0.99±0.06*****	0.87±0.07	1.04±0.13	0.776
DT (ms)	251.6±8.3	226.8±5.6*	257.6±10.4	226.6±7.0*	249.7±15.0	219.1±8.9*	0.997
IVRT (ms)	99.4±3.0	90.8±2.7*	97.8±2.8	88.8±1.7*	96.8±4.3	95.1±4.4	0.191
Tissue Doppler							
E'lat (m/s)	7.82±0.3	8.8±0.3*	7.7±0.4	8.6±0.4*	8.0±0.7	8.2±0.6	0.803
E'septal (m/s)	5.80±0.2	6.3±0.2*	5.8±0.3	6.6±0.3*	5.7±0.5	6.3±0.4*****	0.685
A'(m/s)	9.1±0.4	9.7±0.3	9.5±0.5	9.9±0.3	8.3±0.5	9.2±0.7	0.192
E/E'	10.6±0.5	10.4±0.4	10.4±0.6	10.1±0.4	10.8±1.0	11.0±0.9	0.339
E/E' lat.	9.48±0.5	9.4±0.4	9.4±0.5	9.1±0.4	9.6±0.9	10.1±0.8	0.079

Strain Rate imaging							
SISYS (%)	-17.5±0.41	-18.7±0.35*****	-17.6±0.5	-18.8±0.5*****	-17.5±0.7	-18.7±0.4	0.912
SRSYS (s^{-1})	-0.93±0.03	-0.94±0.02	-0.94±0.03	-0.94±0.03	-0.9±0.05	-0.95±0.04	0.482
SRE (s^{-1})	0.86±0.04	0.90±0.03	0.86±0.04	0.88±0.03	0.87±0.06	0.96±0.06	0.331
SRL (s^{-1})	0.83±0.03	0.85±0.027	0.84±0.04	0.87±0.03	0.83±0.05	0.83±0.04	0.781
SRE/L	1.1±0.06	1.2±0.05	1.1±0.09	1.07±0.06	1.1±0.08	1.2±0.09	0.154
E/SRE (m)	84.0±3.9	84.9±3.3	82.3±4.4	86.0±4.1	87.7±8.3	80.6±5.1	0.114

Values are mean ± SEM. **P ≤0.001, *P≤0.05 between 6 months and baseline value. *P* Value * for difference in **Δ** between responders and non-responders subgroups, the unpaired t-test test was performed.
E/A, the ratio of early (E) to late (A) mitral flow peak velocities; DT = Deceleration time, IVRT = Isovolumetric Relaxation Time. E' septal and E′ lat. = early diastolic peak velocities of mitral annulus at septal and lateral site respectively; E/E' and E/E' lat. = LV filling index; SISYS, systolic strain; SRSYS, systolic strain rate; SRE, strain rate during early diastole; SRL, during late diastole; SRE/L, strain rate early-to-late ratio; E/SRE = E max-to-SRE.

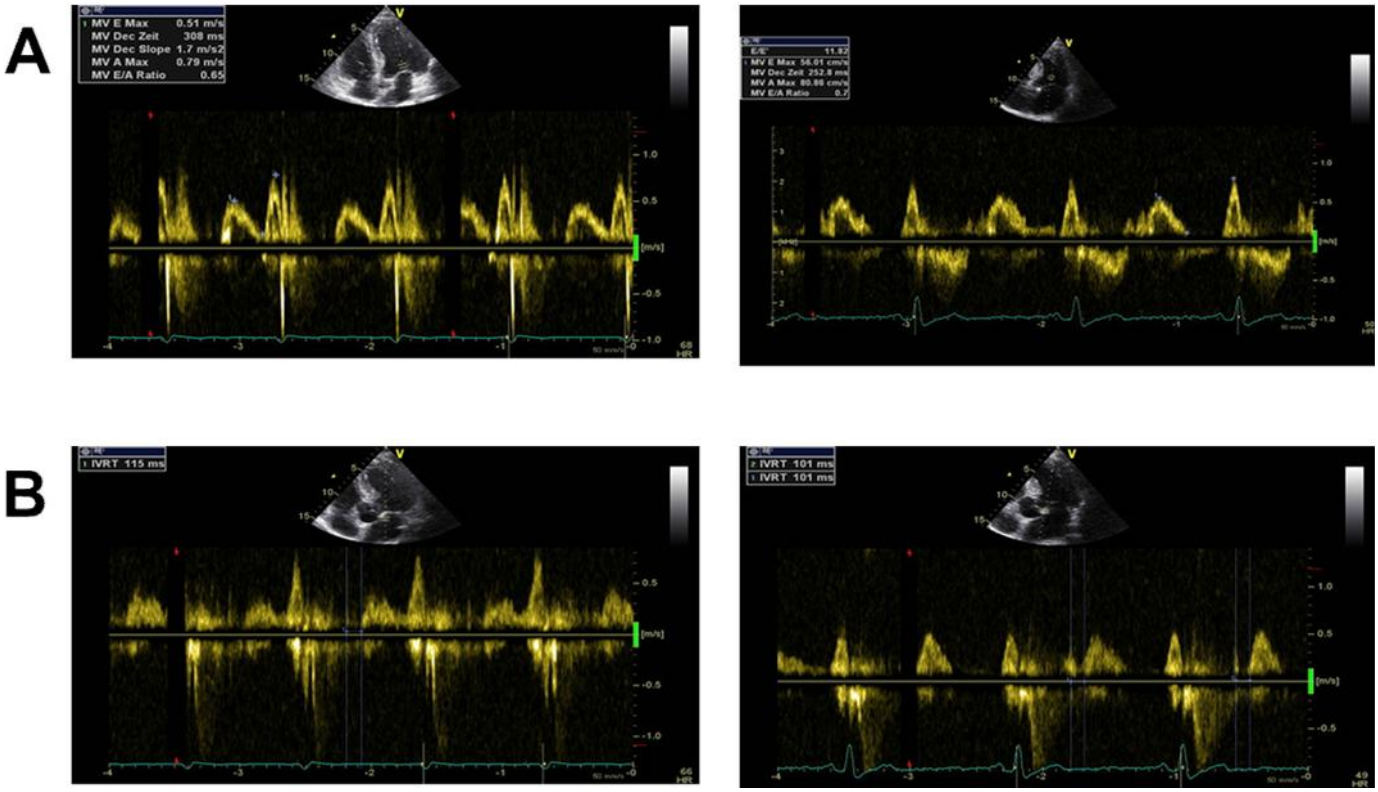


Figure (18): Impact of renal denervation on mitral inflow velocities and isovolumetric relxation time. Improvement in the mitral flow indices (E max, A max, E/A ratio and deceleration time) 6 months after RD compared with baseline (A). Shortening in Isovolumetric relaxation time (IVRT) 6 months after RD compared with baseline (B). Note reduction of HR. See **(Table 6).**

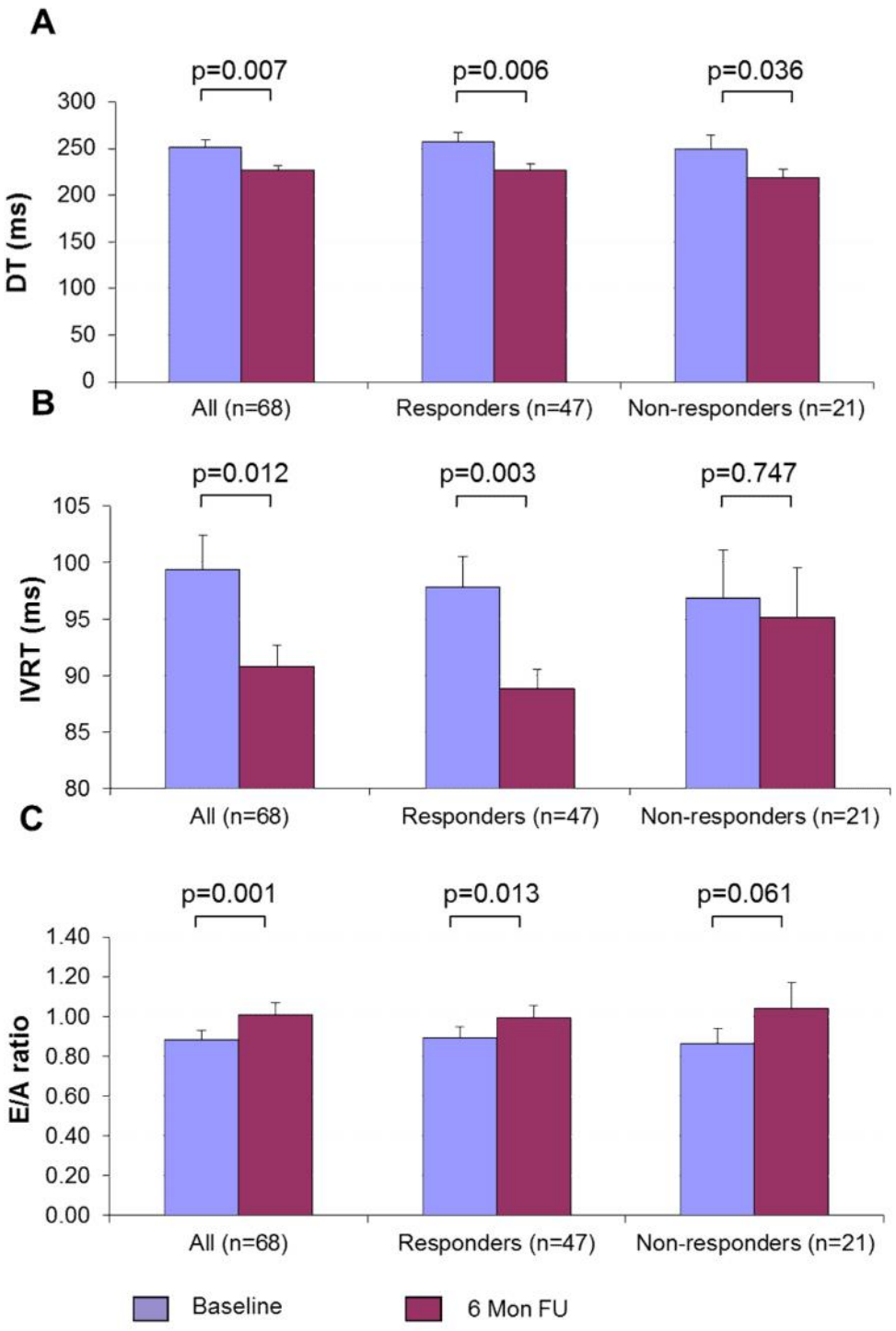


Figure (19): Effect of renal denervation on Doppler derived diastolic parameters; Deceleration time (DT) (A), isovolumetric relaxation time (IVRT) (B) and E/A ratio (C) after 6 months compared with baseline.

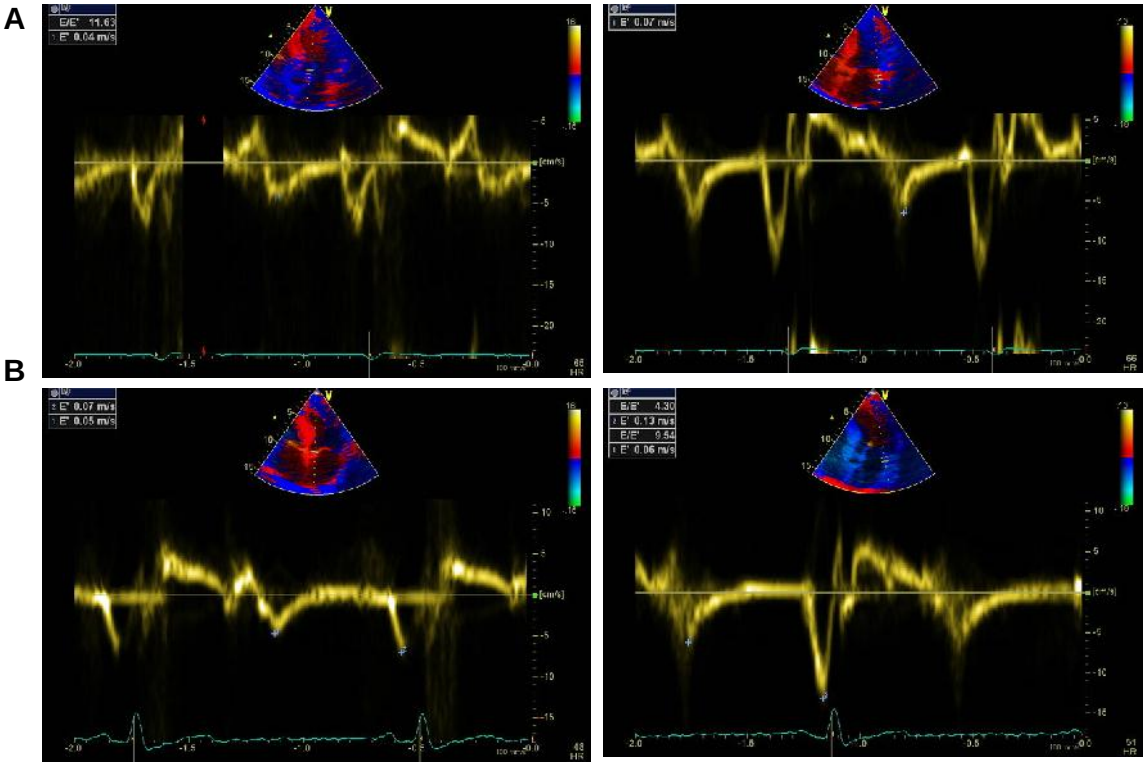


Figure (20): Impact of renal denervation on mitral annular velocities. Septal and lateral mitral annular velocities were recorded from the apical 4-chamber view with the pulse-wave Doppler placed in the septal and lateral corners of the mitral annulus under tissue Doppler imaging mode. Peak early diastolic (E') and late diastolic annular velocities (A') were determined and both E/E' and E/E' lat. were calculated. (A) before RD and (B) after RD. See **(Table 6).**

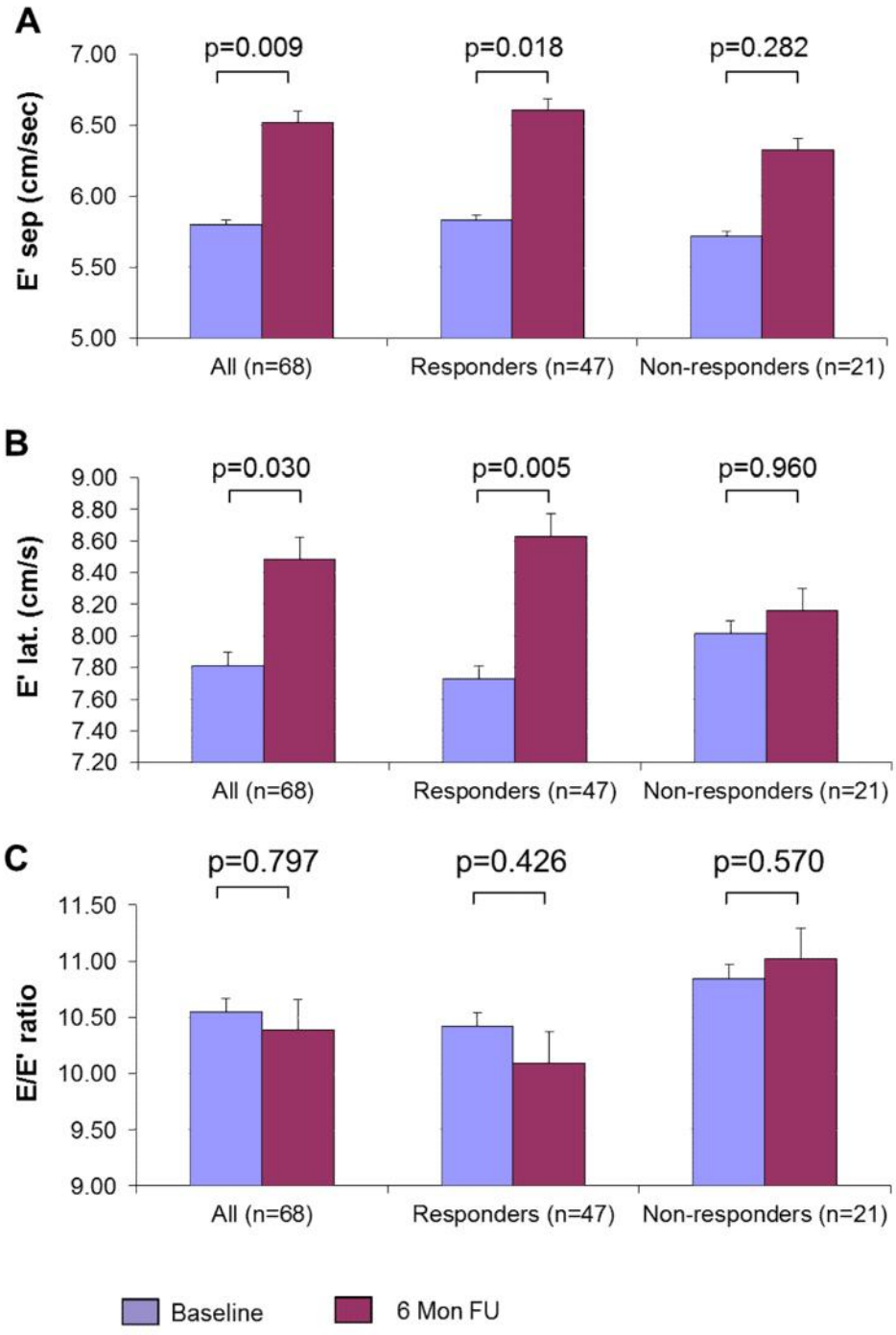


Figure (21): Effect of renal denervation on tissue doppler derived diastolic parameters; E' septal (A), E' lateral (B) and E/E' ratio (C) after 6 months compared with baseline.

7.5.2. Change in Left Ventricular Filling Patterns

E/E’ ratio was used to classify the different patterns of LV filling pressures. It is considered normal if the E/E’ ratio is lower than 8, LV filling pressures are low and considered abnormal if E/E’ more than 15, LV filling pressures is high. Then we considered trans mitral flow parameters to sub classify this abnormal high LV filling pattern in to 3 stages. If DT > 275 ms, IVRT > 105 ms and E/A ratio < 0.5, the patient was diagnosed to have abnormal relaxation (functionally stage 1 diastolic dysfunction). If the previously mentioned trans mitral flow parameters were normal despite the high E/E’ ratio, the patient was diagnosed to have pseudonormalisation pattern (functionally stage 2 diastolic dysfunction). In case of DT < 150 ms, IVRT < 60 ms and E/A ratio > 2, the patient was considered to have restrictive flow pattern (functionally stage 3 diastolic dysfunction). An E/E’ ratio ranging from 8 to 15 is considered suggestive but not a diagnostic evidence of diastolic LV dysfunction and needs to be implemented with trans mitral blood flow to confirm the diagnosis. At baseline, abnormal relaxation had the most common prevalence between patients (37); they represented 54.4%, whereas (24) represented 35.3 % had normal mitral valve flow profile. 7 patients (10.3 %) had pseudonormal flow profile, and no patient had restrictive flow pattern at baseline. After 6 months of treatment, the prevalence of normal flow pattern increased to 47 (69.2%) and abnormal relaxation decreased to 19 (27.9%) and the prevalence of pseudonormal pattern decreased to 2 patients (2.9%), (P=0.027) **Figure (22).**

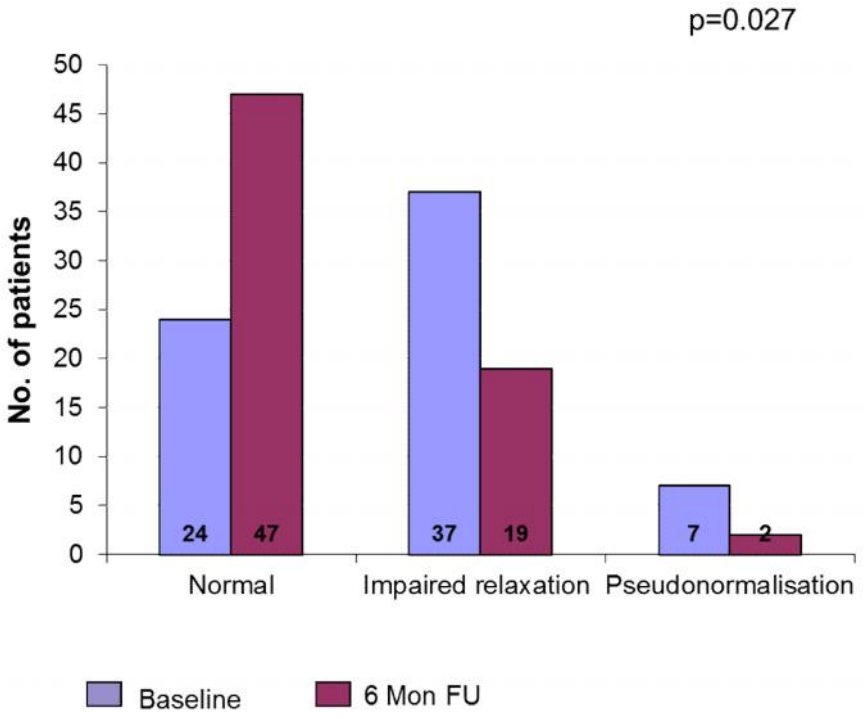


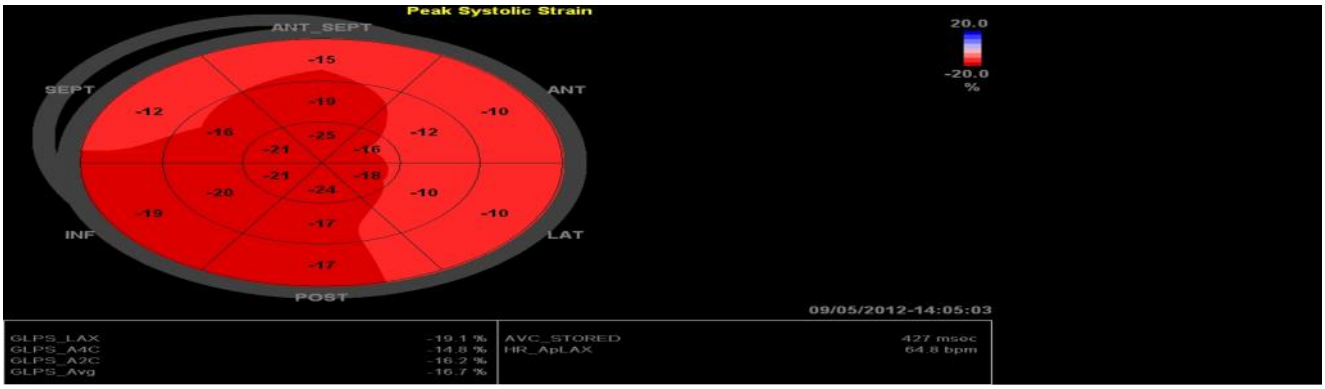
Figure (22): Improvement in Left Ventricular Filling Patterns 6 months after RD compared with baseline. Chi square test was used to find the significance of difference in filling pattern before and after renal denervation.

7.6. Strain and strain rate imaging (SRI)

7.6.1. Systolic SRI parameters

Longitudinal LV systolic function is estimated by mean strain SL and SR. Both represent systolic parameters of SRI. The whole group as well as responders showed significant increase in global longitudinal strain SL (-17.53±0.41 versus -18.65±0.35; *P*=0.003 and -17.55±0.49 versus -18.83±0.84; *P*=0.013, respectively) **Figures (23 and 24)**. In contrast, GSR did not show significant differences between FU and baseline. 6 months after RD, non-responders showed no observed significant improvement in global longitudinal systolic SRI parameters **(Table 6)**.

A



B

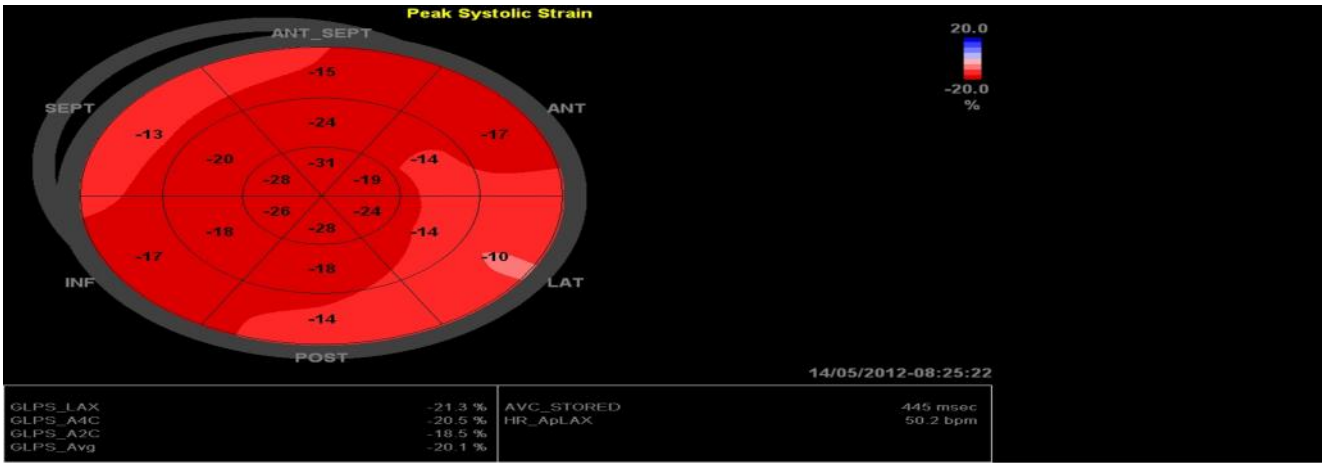


Figure (23): Global longitudinal strain (Bull`s Eye) before (A) **and 6 months after RD** (B).

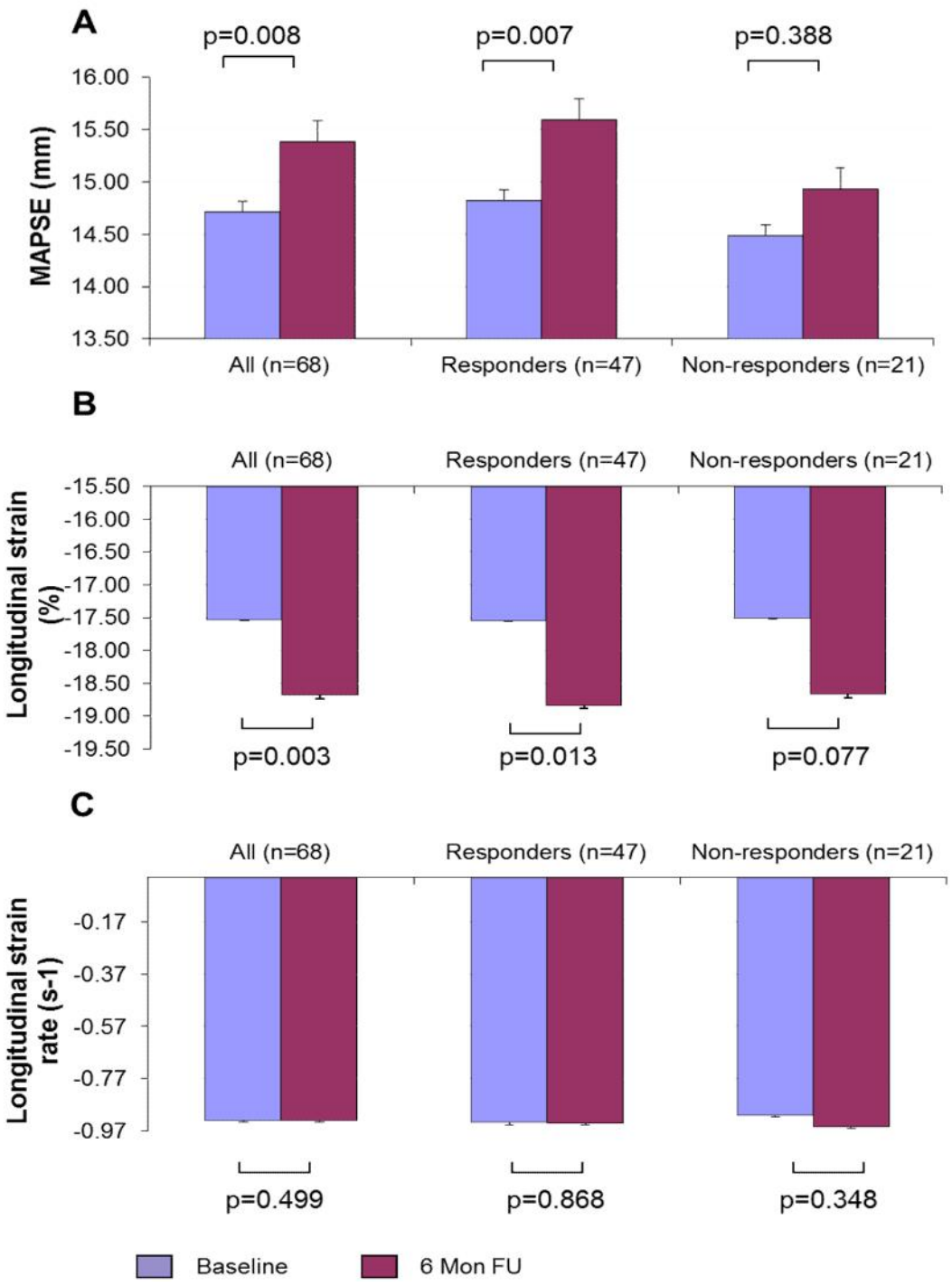


Figure (24): Effect of renal denervation on Mitral annular systolic excursion (MAPSE) (A), longitudinal strain (B) and longitudinal strain rate (C) after 6 months compared with baseline.

7.6.2 Diastolic SRI parameters

When we studied the diastolic parameters derived from SRI, we found improvement of the early and late diastolic parameters (SRE and SRL) in whole group as well as responders but that was statistically non significant **Figures (25 and 26)**. In a trial for more understanding of the effect of RD on LV diastolic function, we analyzed standard and strain-derived diastolic parameters in the patients who had diastolic dysfunction (DD) at baseline (42 patients) defined according to conventional Doppler parameters for LV diastolic function. Regarding the conventional parameters derived from trans mitral flow and TDI, we found significant increased E/A ratio after 6 months (0.81±0.06 versus 0.89±0.05; *P*=0.007) with significant shortening in deceleration time (DT) and isovolumetric relaxation (IVRT) from baseline values (-43.26±11.63 ms; *P*=0.0006 and -8.14±3.57 ms; *P*=0.028 respectively). However, no significant improvement involved E/E' or E/E' lat. was found in this subgroup, similar to the whole group and responders subgroup **Figures (27)**.

When we looked closely to SRI parameters, we found significant increase involved global SL (-17.05±0.55 versus -18.71±0.47; *P*=0.0004) and the early strain rate diastolic parameter (SRE) (0.80±0.05 versus 0.89±0.04; *P*=0.009) in patients with DD at baseline. There as a trend for an increase in global SR but it was statistically non significant (-0.92±0.04 versus -0.96±0.03; *P*=0.093) **Figure (28)**.

Among all these mentioned diastolic parameters, patients with no evidence of DD at baseline showed only weak significant increase in E/A ratio after RD (0.20±0.10; *P*=0.051). DT as well as global longitudinal systolic strain rate (SR) in this sub group both tend to deteriorate with a significant difference between the change in both DT and SR between both groups (*P*= 0.0006 and *P*=0.038 respectively).

A

B

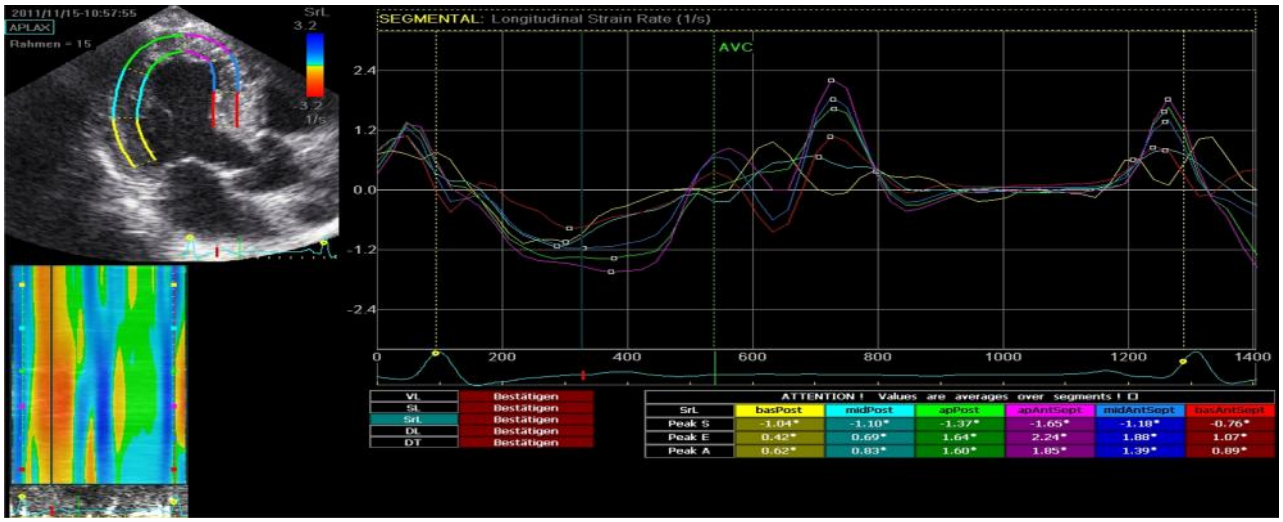


Figure (25): Systolic and diastolic strain rate before (A) **and 6 months after RD** (B) involving segments of 3 champers view (apical long axis view) .

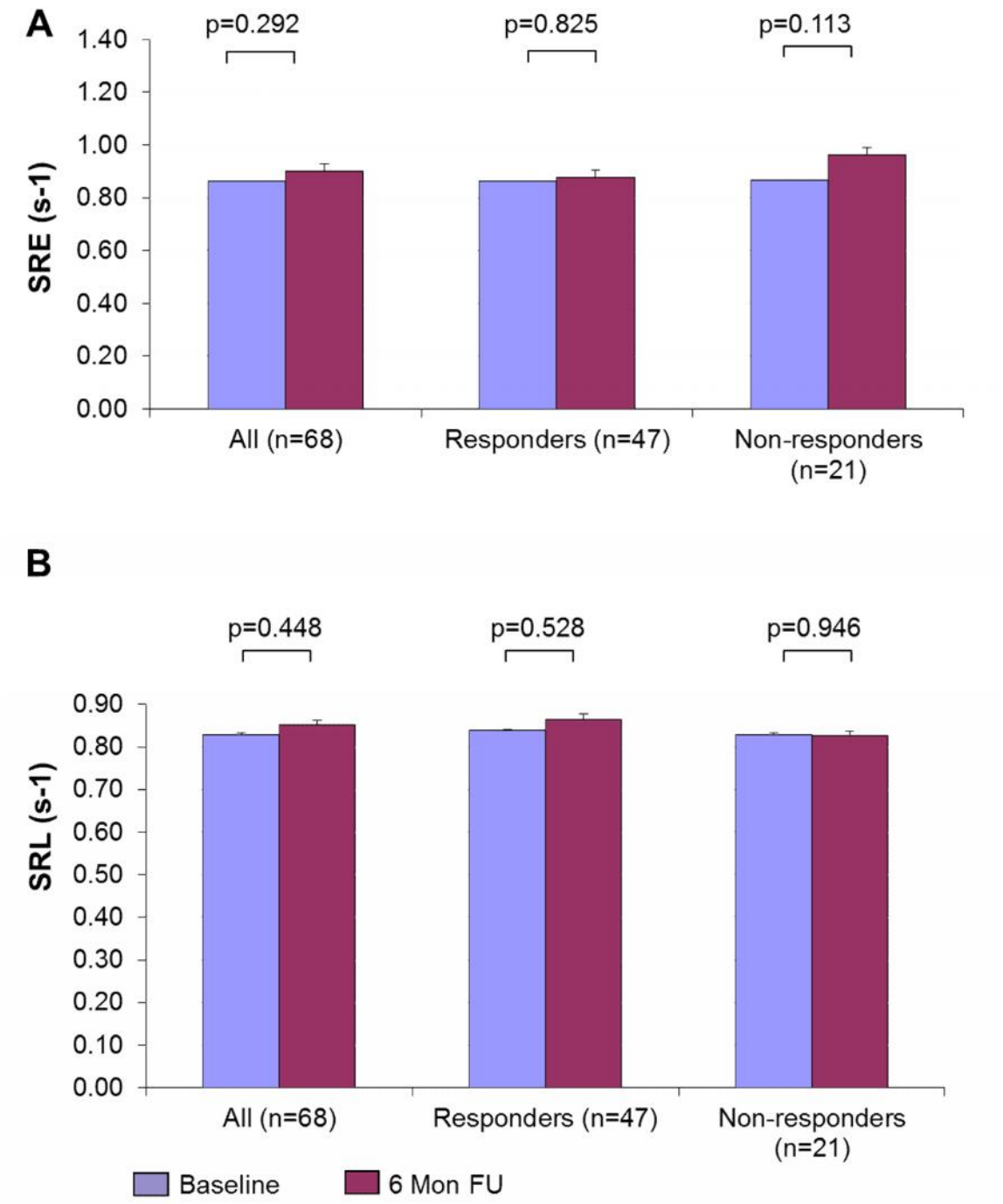


Figure (26): Effect of renal denervation on early diastolic strain rate SRE (A) and late diastolic strain rate SRL (B) after 6 months compared with baseline.

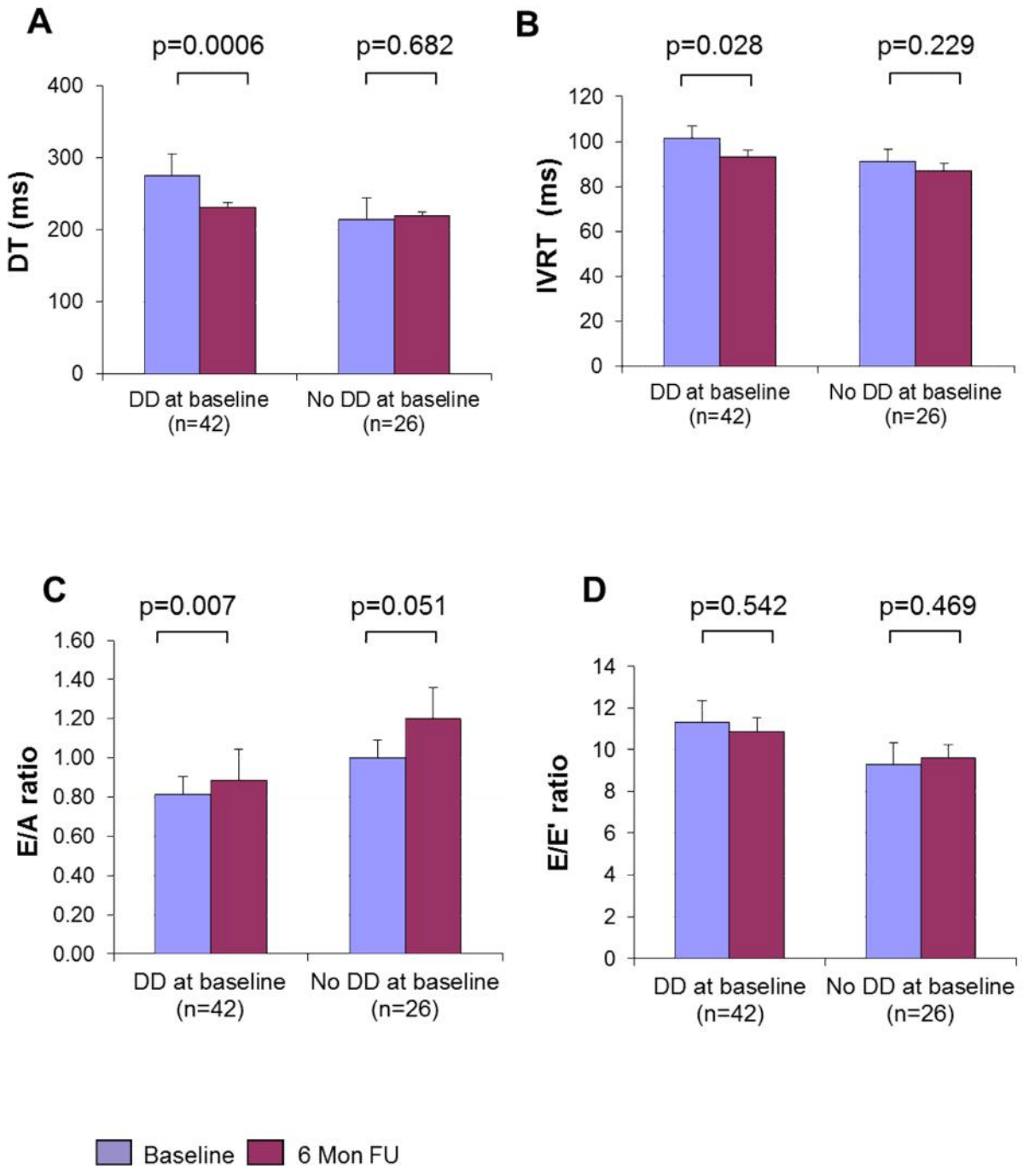


Figure (27): Impact of renal denervation on deceleration time (A), isovolumetric relaxation time (B), E/A ratio (C) and E/E' ratio (D) after 6 months compared with baseline in patients with resistant hypertension divided according to the existence of diastolic dysfunction at baseline. DD: diastolic dysfunction.

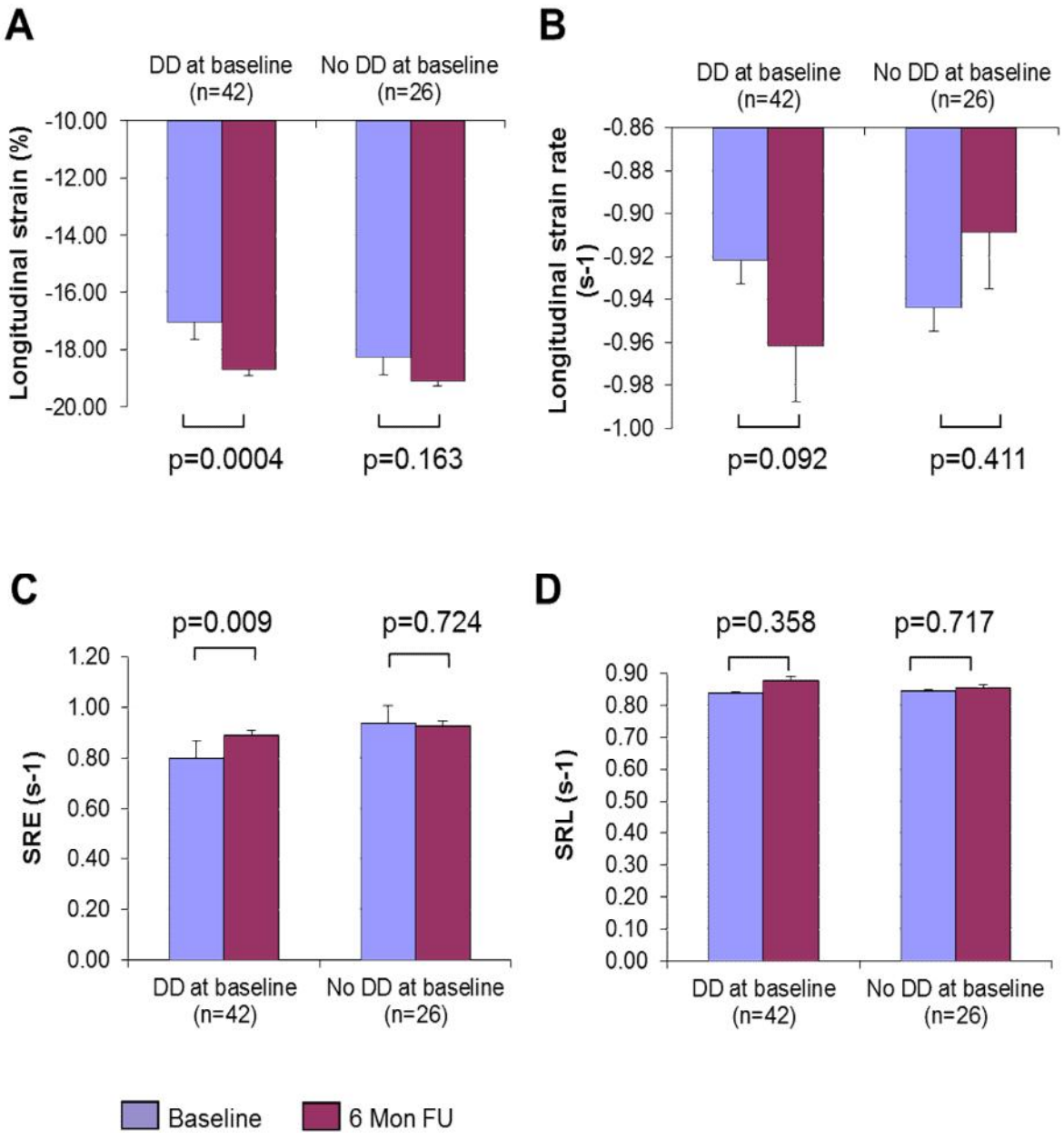


Figure (28): Impact of renal denervation on strain rate imaging derived systolic parameters; global longitudinal strain (A), global longitudinal strain rate (B) and diastolic parameters; early diastolic strain rate (C) and late diastolic strain rate (D) after 6 months compared with baseline in patients with resistant hypertension divided according to the existence of diastolic dysfunction at baseline. DD: diastolic dysfunction.

7.7. Linear correlation results between changes in different parameters 6 months after RD

Correlation coefficient (r) **(Table 7)** was calculated of the following parameters

7.7.1. Correlation between changes in systolic and diastolic SRI parameters Figure (29)

The increase in both global SL and systolic SR was found to be correlated positively (r = 0.65; P <0.0001). On the other hand, the increase in global SL (systolic strain parameter) correlated with the changes in diastolic strain rate parameters (SRE, SRL and E/SRE) (r = 0.72, 0.43, - 0.53 respectively; P<0.0001). Linear correlation also showed that the increase in SR, as also a systolic parameter, is positively correlated with changes in diastolic SRI parameters namely SRE (r = 0.38; P<0.0001), SRL (r = 0.44; P<0.0001) and negatively with E/SRE (r = - 0.409; P<0.0001).

7.7.2. Correlation between changes in diastolic parameters derived from SRI and changes in the standard conventional diastolic parameters

It was found that the increase in the early diastolic parameter derived from SRI (SRE) correlated positively with both the increase in the early diastolic parameter derived from trans mitral blood flow (E max) (r = 0.30; P=0.016) and the increase in E/A ratio (r = 0.25; P = 0.050). Similarly, SRE was found to be positively correlated with E' lat., as a diastolic parameter derived from TDI, (r = 0.37; P=0.003). Interestingly, it was found that the increase in SRE/SRL ratio correlated positively with the increase in E/A ratio (r = 0.47; P<0.0001) **Figure (30)** and negatively with DT (r = - 0.25; P= 0.05). On the other hand, the increase in E/SRE ratio (derived from SRI) found to be negatively correlated to the shortening in IVRT(r = - 0.25; P=0.053) but it was found to be positively correlated with increased in both E/E'(r = 0.45; P<0.0001) **Figure (31)** and E/E' lat. (both derived from TDI assessment of diastolic function) (r = 0.33; P= 0.011).

7.7.3. Correlation between the changes in global systolic SRI and LV parameters

We found that the increase in global SL (longitudinal systolic parameter derived from SRI) correlated positively with the increase in MAPSE which is considered also as longitudinal systolic function parameter measured by 2D echocardiography (r = 0.27; P = 0.033) and negatively with the regression in LV mass index in response to RD (r = - 0.26; P = 0.041). The change in LVEF, as assessed by biplane Simpson's method, also correlated positively with the increase in MAPSE (r = 0.33; P=0.008) without observed significant correlation between it and the changes involved SRI systolic parameters 6 months after RD.

7.7.4. Correlations between different other parameters in response to treatment of resistant HTN using RD

MAPSE, was found to be positively correlated with late diastolic parameter derived from trans mitral flow (A max). The same also was found between regression of LVEDV and increase in E' lat., diastolic parameter derived from TDI, (r = 0.27; P = 0.031). This increase in E' lat. was found to be positively correlated with the increase in the global SL (r = 0.35; P = 0.005). In contrast, increase in early diastolic SRI parameter (SRE) was detected to be negatively correlated with reduction in LV mass (r = - 0.27; P = 0.033). Shortening in DT was observed to be positively correlated with reduction in DBP (r = 0.36; P = 0.001). Similarly, decrease of LAVI was positively correlated with reduction of SBP which considered statistically weak positive correlation (r = 0.23; P = 0.051). Except that, no observed correlations were found between the different echo parameters and the reduction of BP or HR.

Table (7): Correlation coefficient between changes of different parameters after renal denervation

Character	Δ SL%	Δ SR	Δ SRE	Δ SRL	Δ SRE/L Ratio	Δ E/SRE	Δ DT	Δ E'lat	Δ LAVI
Δ SBP	0.050	0.225	0.124	-0.060	0.145	-0.179	0.048	-0.025	0.231*
Δ DBP	0.086	0.136	-0.093	-0.084	-0.010	-0.115	0.360**	-0.034	0.124
Δ SL%	…..	0.649**	0.718**	0.427**	0.231	-0.53**	-0.113	0.350**	0.152
Δ SR	……	…..	0.381**	0.441**	-0.058	-0.409**	0.077	0.235	0.024
Δ SRE	……	……	……	0.249*	0.587**	-0.575**	-0.248	0.373**	0.155
Δ E max	0.201	0.036	0.304*	-0.067	0.385**	0.468**	-0.329**	0.405**	0.038
Δ Amax	0.198	0.009	0.131	0.242*	-0.109	0.081	-0.275*	-0.068	0.012
Δ E/A ratio	0.072	-0.004	0.247*	-0.222	0.469**	0.219	-0.045	0.298*	-0.005
Δ E/E' ratio	-0.038	-0.093	0.004	-0.176	0.167	0.453**	-0.242	-0.305*	-0.043
Δ E/E'lat ratio	-0.061	-0.068	-0.003	-0.129	0.134	0.325*	-0.238	-0.498**	0.017
Δ MAPSE	0.267*	0.146	0.072	0.149	-0.044	-0.113	0.216	0.050	0.081
Δ LVMI	-0.261*	-0.157	-0.216	-0.074	-0.098	0.115	-0.014	-0.168	0.042

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).
SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, LVMI = Left Ventricular Mass Index, LVEDvol = Left Ventricular End Diastolic Volume, LAVI = Left Atrial Volume Index, MAPSE = Mitral annular plane systolic excursion, E/A, the ratio of early (E) to late (A) mitral flow peak velocities; DT = Deceleration time, E′ lat. = early diastolic peak velocities of mitral annulus at lateral site; E/E′ and E/E′ lat. ratios = LV filling index; SL, systolic strain; SR, systolic strain rate; SRE, strain rate during early; SRL, during late diastole; SRE/L, strain rate early-to-late ratio; E/SRE = E max-to-SRE.

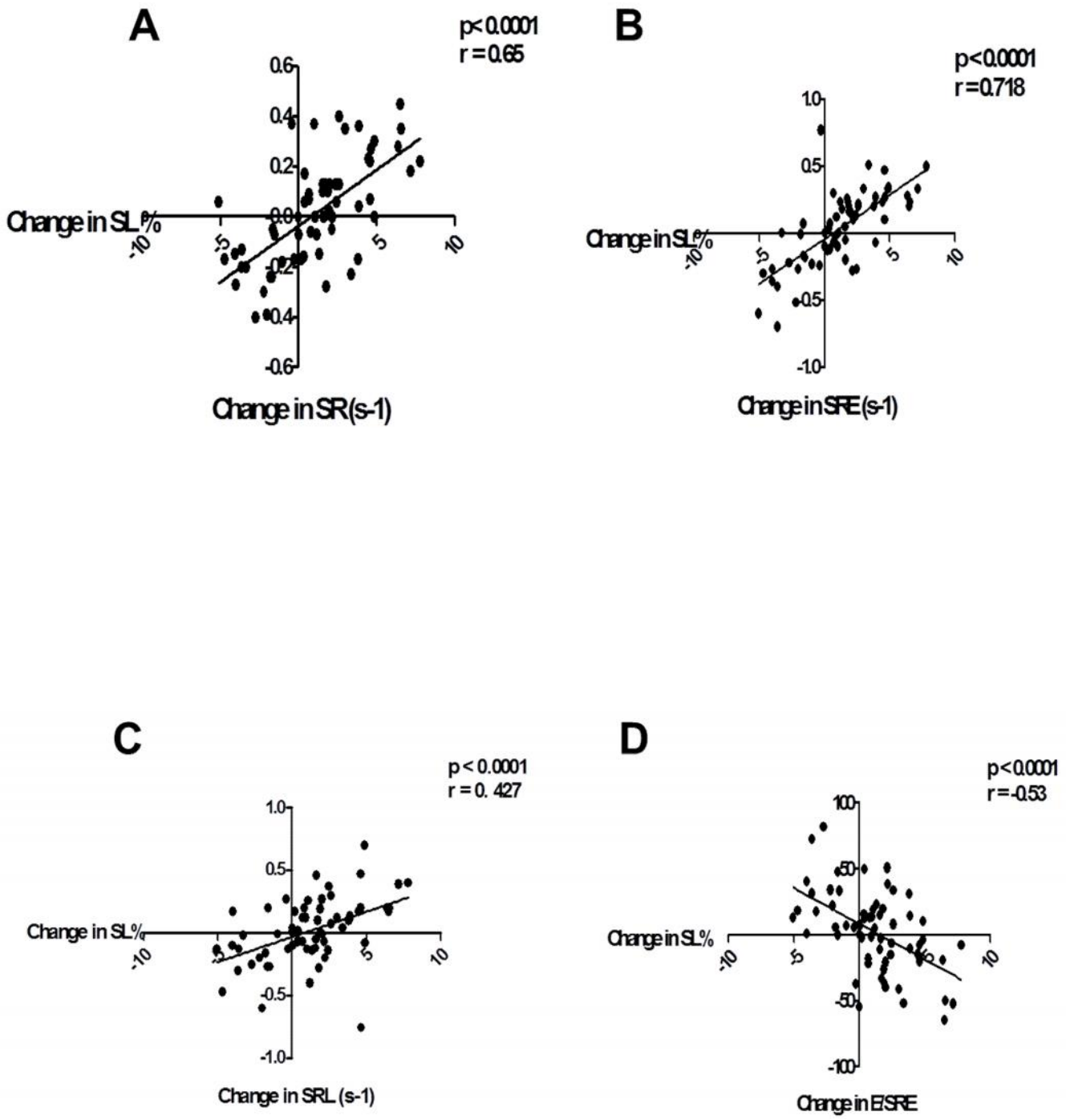


Figure (29): Correlation coefficient between changes in systolic strain and diastolic strain rate imaging parameters 6 months after renal denervation.

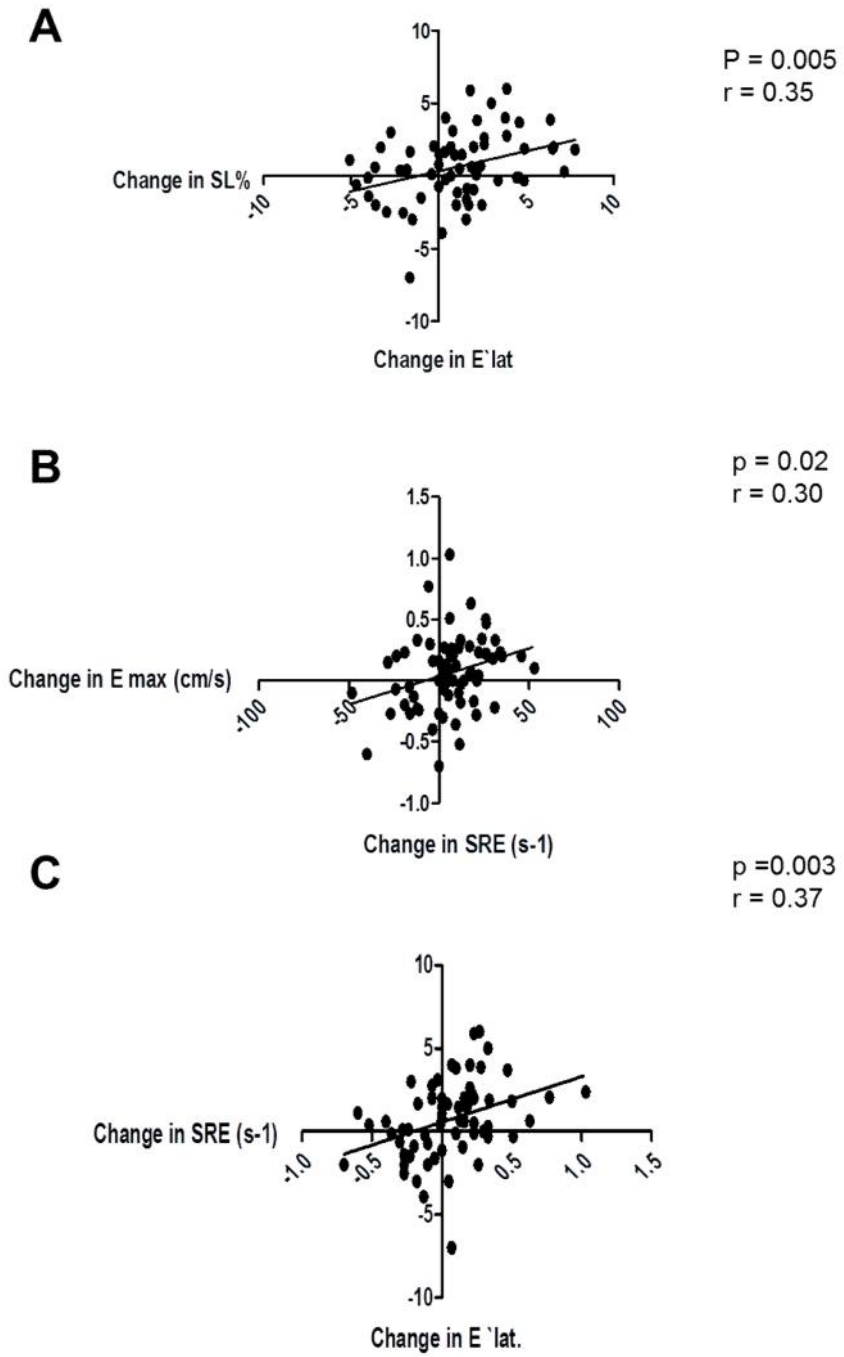


Figure (30): Correlation coefficient between changes in strain rate imaging parameters and changes in some standard diastolic parameters 6 months after renal denervation.

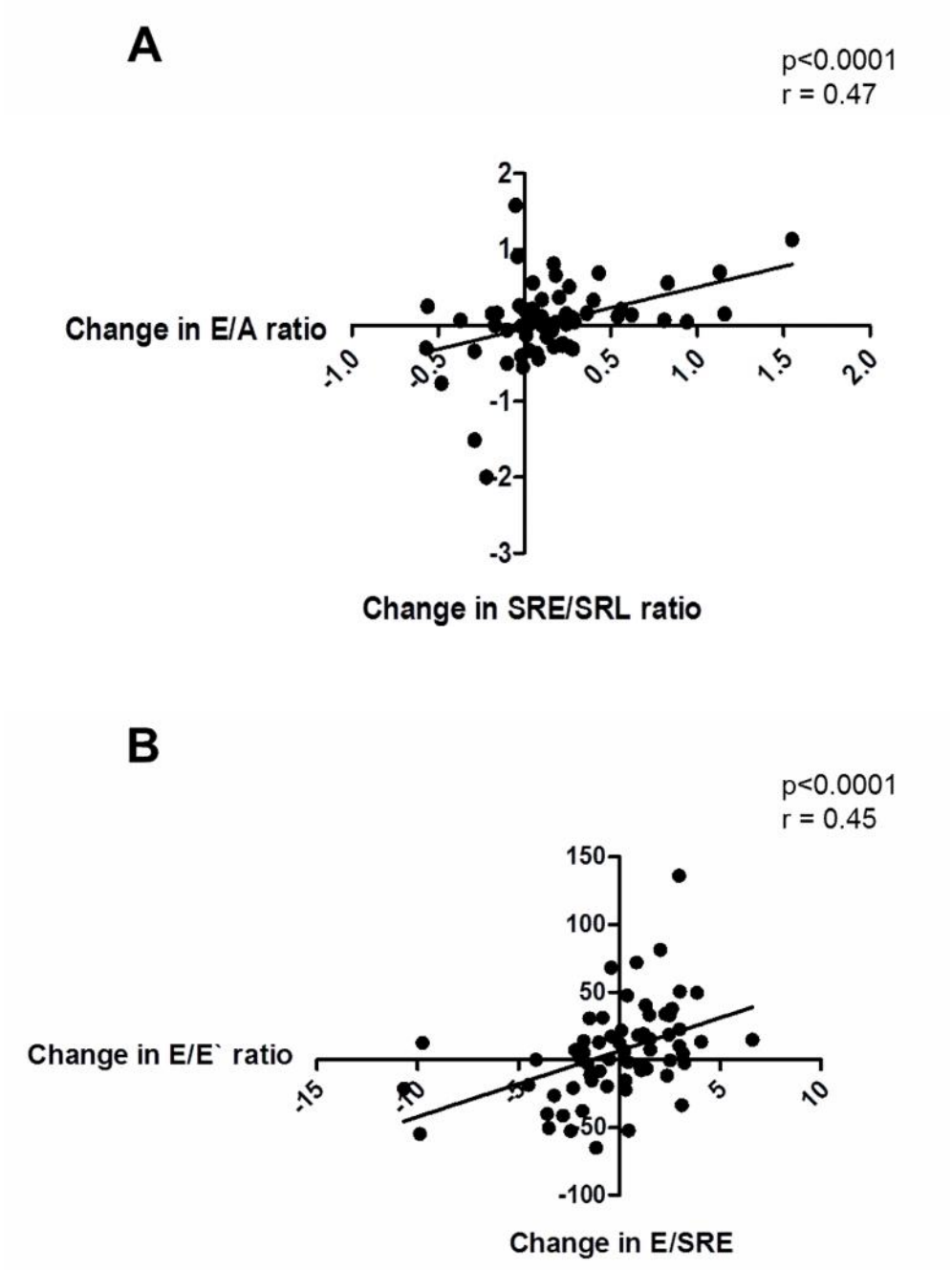


Figure (31): Correlation coefficient between changes in standard diastolic ratios and changes in diastolic ratios derived from strain rate imaging 6 months following renal denervation.

8. Discussion

We analyzed in the current study the effect of denervation of the renal sympathetic as treatment of resistant HTN on hypertension-related cardiac remodeling and functional impairment. In addition to the BP-lowering effect, we were able to observe reduction of LV mass, LA volume, improvement of systolic and diastolic parameters by using conventional 2D echocardiography, Doppler and longitudinal strain derived from 2 D echocardiography speckle tracking. The improvement observed after 6 months follow-up period. Reduction of peripheral BP was the main target in the treatment of patients with arterial hypertension for many years. Recently, the evidence is increasing indicates that the mode of BP control may differentially affect outcome (Lindholm et al., 2005 and Williams et al., 2006). It has been observed that reduction in cardiovascular morbidity and mortality does not automatically follow the lowering of peripheral BP as a main target (De Caterina et al., 2010). It is still affected by other confounders mainly LVH as intermediate endpoint which is shown to be reliably linked to cardiovascular prognosis (Devereux et al. 2004 and Pierdomenico et al., 2010).

8.1. Effect of RD on hemodynamics

Chronic stimulation of the sympathetic nervous system is responsible for the development and maintenance of arterial hypertension (Sobotka et al., 2011) and it is a key component of the signalling pathways altered in hypertension-related cardiac remodeling (Mancia et al., 2010). The Simplicity trials (HTN-I and HTN-2) identified a significant and safe reduction in blood pressure achieved with catheter-based renal denervation in patients with resistant HTN which provided insights into the critical role of renal sympathetic and somatic nerves in mediating resistant hypertension (Simplicity HTN-I by Krum H, et al., 2009 and Symplicity HTN-2 Investigators. 2010).

In our study, we noticed a significant reduction of the blood pressure in the whole group. We further subdivided the patients according to the pattern of response into two sub group, in which the response was defined as reduction of SBP$\geq$10 mmHg. Until now, we cannot predict which population will respond satisfactory to RD. Heart rate (HR) is a

predictor of cardiovascular mortality and morbidity in the general population, as well as in patients with hypertension and heart failure (Kolloch et al., 2008, Böhm et al., 2010 and Reil et al., 2011).

Beside BP lowering effect, our findings indicate a reduced resting HR in whole group after RD. That was independent on BP response as both responders and nonresponders also showed a significant decrease in resting HR. This finding confirms recent studies analysing the effect of RD on HR at rest (Ukena et al., 2011 and Brandt et al., 2012).

Reduction of HR in patients who lack a relevant reduction of BP suggests that also in BP non-responders there is a relevant anti-sympathetic effect of RD.

8.2. Effect of RD on different echocardiographic parameters

Many echocardiographic findings were significantly improved between BP responders and non-responders, in comparison with baseline. However, there was a trend of BP nonresponders to have maintained high BP and to show even deterioration in few cardiac systolic and diastolic parameters.

8.2.1. Regression of the left ventricular hypertrophy

The presence of LVH, as an indicator of end-organ damage, is associated with an increased rate of cardiovascular events and death independent of other cardiovascular risk factors and, notably, independent of BP values (Ruilope et al., 2008 and Bombelli et al., 2009). The sympathetic nervous system mediates hypertension-induced hypertrophy via direct stimulation of cardiomyocyte beta-adrenergic receptors as prove with experimental evidence (Perlini et al., 2005). Cardiac fibrosis and inflammation have been provided to be a result from mast cell stimulation, activation of afferent sympathetic nerves, angiotensin II production, and norepinephrine release, rather than being mediated via alphaadrenergic receptors (Levick et al., 2010).

In hypertensive rat models both beta-blockade and sympathectomy attenuated LVH, whereas accompanying myocardial interstitial fibrosis was abolished by sympathectomy

or doxazosin but left unchanged by beta-blockade (Perlini S, et al., 2005). These experimental results were further supported by clinical observations. Antihypertensive treatment with angiotensin receptor antagonism (losartan) has superior efficacy for reversing LVH, a cardinal manifestation of hypertensive target organ damage, than conventional atenolol-based treatment as demonstrated in The LIFE study (Losartan Intervention For Endpoint reduction in Hypertension) (Dahlof et al., 2002).

In our study, we obtained a pronounced reduction of the LVMI by 19 gm/ m² (- 15% from baseline) after RD, indicating a more pronounced effect of RD on LV mass regression and LVH reduction in this treatment resistant patient group compared with the effect of different antihypertensive drug classes used for treatment of uncomplicated hypertension (Klingbeil et al., 2003). This finding was also found in both involved subgroups in our study which denotes that the regression, following RD, was found regardless of BP response after the procedure. This supports the hypothesis of BP-independent effects of RD on LVH which was observed with animal models, in which LV mass regression occurred also in 5 of 6 sympathectomy "nonresponders" (Perlini et al., 2005). This was also further approved by a meta-analysis demonstrating that beta-blockers induced significantly less LVH regression compared with various other antihypertensive drugs, especially blockers of the rennin-angiotensin system beyond the effects of BP reduction (Dahlof et al., 1992). That might explain, why there was no observed significant correlation between changes in LVMI and changes in SBP or DBP in our study. Recently, Brandt et al 2012 studied the effect of RD on LV mass and detected the significant reduction of LV mass index in the group received RD but not in the control group, who did not receive RD as a therapy for resistant HTN.

Catheter-based RD reduces noradrenaline surge by reduction of the renal sympathetic efferent activity (Krum et al., 2011). Furthermore, by the ablation of afferent renal nerves, which stimulate sympathetic outflow in the hypothalamus, the whole-body sympathetic activation is also reduced (Schlaich et al., 2009). Thus, in contrast to beta-blockers, RD diminishes both beta- and alpha-receptor–mediated sympathetic hyperactivity. It was not possible to distinguish how these changes resulted from RD, but the aforementioned signaling pathways, at the end, lead to decrease pressure overload,

which probably contributed to diminish LVEDD in both sub-groups. The later contributes mathematically to the calculated LV mass index.
We conclude that RD promotes LVH regression independent on BP reduction effects.

8.2.2. Effect of RD on diastolic function

The term diastolic dysfunction refers to an abnormality of diastolic compliance, filling or relaxation of the left ventricle, regardless of whether the patient is symptomatic or not and whether the EF is normal or abnormal (Greenberg et al., 2002). Increased afterload increases mechanical stress, which provokes collagen synthesis and LVH through internal mechanisms and production of some mediators (Komuro et al., 1991). Increased percentage of myocardial collagen seems to be the main underlying cause of DD of the LV. That is noticed in hypertensive patients with or without LVH (Gottdiener 1993). Left ventricular diastolic dysfunction often occurs before systolic dysfunction in patients with HTN (Poulsen et al., 2003). In addition, asymptomatic DD is reported to be present in 40–60% of those patients with coronary artery disease, hypertension, valvular heart disease, hypertrophic cardiomyopathy, diabetes, or cardiac amyloidosis, who develop heart failure with apparently normal global systolic and diastolic functions of LV on conventional echocardiography (Vasan et al., 2000). LV diastolic dysfunction has been recognized as an important primary cause of heart failure (Weidemann et al., 2002). Several studies indicated a close relation between refractory hypertension and LVH, as well as LVH and DD (Diez et al., 2002 and Salles GF et al., 2010). Unfortunately there is no clinical way to assess accurately the amount of collagen in the LV. Left ventricular diastolic function might reflect, in part, the degree of fibrosis in the myocardium and it is a potential means of measuring myocardial stiffness, relaxation and determination of LV filling pressures (Nagueh SF et al., 2009). Doppler parameters usually used in our daily practice to assess the diastolic function of the LV. Besides inducing LVH regression, RD in our study resulted after 6 months in a 6.7% shortening IVRT, 18 % increases in E/A ratio and 10% reduction in mitral valve deceleration time in all patients received RD as a treatment of resistant HTN. Similar response was found concerning the same diastolic

parameters in responders. It was also found a significant positive correlation between the reductions in DT and the reduction in DBP in the whole group after 6 months from RD.

Regarding the non-responders, they showed only significant shortening of DT with out any observed significant changes involving the other Doppler parameters despite LVH regression. E/E` ratio, as an LV filling pressure parameter was not significantly changed after RD in our study.

The results of antihypertensive treatment on LV diastolic function are also conflicting. Regression of LVH has been associated with preserved, (Zakynthinos et al. 2004) improved, (Trimarco et al., 1989, White et al., 1989, Gottdiener 1991 and Muiesan et al., 1991) or even deteriorated (Sen et al. , 1979) diastolic LV filling after antihypertensive therapy.

Looking to our patients, the responders showed better improvement in Doppler diastolic parameters, as actually expected, than non responders although the later showed a significant DBP reduction but that did not corresponding to criteria of response. It is proved that the decrease of the pressure overload per se affects myocardial collagen content and probably normalizing connective tissue in response to antihypertensive treatment. (Little et al., 1995 and Mizushige et al., 2000) and will lead to improvement of active relaxation and reduction of passive chamber stiffness (Ohno et al., 1994). Reduction of Doppler diastolic parameters in our patients corresponds well with what is found in animals (Dussaillant et al., 1996), patients with aortic stenosis and aortic valve replacement (Villari et al., 1995), and in response to ACE Inhibitors and ARBs as antihypertensive agents (Klingbeil et al., 2000, Verdecchia et al., 2000 and Zakynthinos et al., 2004). In these studies, also the LV filling pressures, represented by E/E`, did not show change after therapy in spite of the reduction in LVMI. They observed that the changes in diastolic stiffness and LV filling pressure depend more on myocardial collagen than it does on myocardial mass (Dussaillant et al., 1996) in which the decrease in hemodynamic overload and the reverse of myocardial remodeling have been associated with a decrease in muscle mass but associated with a relative increase in

fibrous tissue. Fibrous tissue regresses less rapidly than myocardial tissue, necessitating 7 years for normalization of myocardial stiffness in one study (Villari et al., 1995).

A potential impact of RD on myocardial fibrosis remains speculative. Experimentally, a central inhibition of the SNS rapidly reduces cardiac hypertrophy and improves relaxation without any observed effect on LV filling pressures in hypertensive rabbits. (Signolet et al., 2008). On the other hand, Brandt et al 2012 supported that RD significantly improved tissue-Doppler derived LV filling pressures. In our study, due to the simultaneous increase in both E and E` values, the overall E/E` ratio remained eventually unchanged.

We conclude that improvement of diastolic parmeters following RD was mainly prominent in responders' population.

8.2.3. Effect of RD on LA volume

Left atrial enlargement is considered as an early sign of hypertensive heart disease in patients with no other discernible cause (Culpepper et al., 1983). It is also a powerful independent risk factor for stroke, atrial fibrillation and congestive heart failure (Verdecchia et al., 2003, Gerdts et al., 2007 and Kim et al., 2009).

LA enlargement in hypertensive patients is a complex and multi factorial phenomenon (Lind et al., 1995). It could be affected by changes in LV systolic and diastolic function. It is well established that LA reservoir and pump functions are increased in hypertensive patients with LVH and impaired LV relaxation (Erol et al., 2001) as impairment in LA function associating LA remodeling process. The prevention of LA enlargement should be based on a comprehensive strategy addressed mainly at reducing the development of LVH or at promoting its regression and at controlling high blood pressure. (Lind et al., 1995).

LA may not enlarge in a symmetrical fashion, and any or all three of its orthogonal axes may increase at rates greater than the others. Hence, the use of a single linear dimension may not accurately reflect either LA volume or its change (Pritchett et al., 2003). In the present study, LA volumes were measured echocardiographically according to a biplane

method combining measures obtained from four chamber and two-chamber apical views and then LAVI was calculated.

We found that all patients, including both sub groups, showed a significant reduction in LAVI (all 11%, responders 9.6% and non responders 9.4 % respectively) after renal artery ablation.
A positive correlation also found between reduction in LAVI and the reduction in SBP in all our patients. Cuspidi et al, found the high SBP was independently correlated to LA size (Cuspidi et al., 2005).
In our patient, LA enlargement at the baseline was associated with abnormal conventional diastolic parameter. BP reduction beside regression of LVMI and reduction of LVED volume and dimension were reported. Reduction in LA size was found to be associated all these changes in our study.

Simek et al., 1995 reported that LA volume and function are important determinants of LV filling particularly when LV compliance is reduced, which is the case with LVH. It was also observed with telmisartan that a reduction of LV end-diastolic pressure and regression of LVMI were associated with an increase in diastolic filling and with a significant reduction of active and passive emptying contribution of left atrium to LV stroke volume (Mattioli et al., 2005). Beside that, we recorded in our study a regression of most of diastolic function parameters, which was significantly prominent in responders. That suggests an improvement in both impaired relaxation and abnormal high passive stiffness of the LV. All these factors together reflected on LA size and functions and might also contribute to the reverse of LA remodeling process after RD which has been recently observed (Brandt et al., 2012). We can conclude that modification of LV geometry and reduction of LV end-diastolic pressure and volumes after RD, express the reduction of LA volumes. This also associated with the significant improvement of the diastolic filling parameters that related to active relaxation and passive chamber stiffness in responders. Reduction of LA size might also reflect an early improvement of LV relaxation and stiffness in non responders even if there no significant improvement in

Doppler parameters was recorded, in which the utility and accuracy of Doppler parameters could be limited. (Nagueh SF et al., 2009).

8.2.4. Effect of RD on systolic function

Several studies determined that the systolic function of the heart did not change with antihypertensive therapy. This is in keeping with data demonstrating that the systolic function of the heart is well preserved in patients treated with angiotensin receptor blocker (Losartan), despite the decrease of LV mass (Klingbeil et al., 2000, Verdecchia et al., 2000 and Omvik et al., 2000). Although the LVED volume improved significantly in our patients on top of relieving the afterload, but this did not contribute to LVEF which did not show significant change in our study.

As long as we have not enough available data determining the effect of RD on myocardial structure and function so we could not understand perfectly the effect of RD on LV systolic function. However, certain echocardiographic parameters e.g MAPSE, GSL and GSR are helpful to analyse the effect of RD on LV systolic function. These parameters reflect the state of longitudinal systolic function of LV, which considered an element of the global LV systolic function.

Long-axis myocardial systolic function is impaired first (Henein et al., 1998) as seen in different pathologic conditions (e.g., myocardial ischemia or hypertrophy). Also, echocardiographic analysis of longitudinal myocardial function could help in early diagnosis of early cardiac systolic dysfunction, especially in patients with normal global systolic function and EF. (Vinereanu et al., 2005 a and Elnoamany et al., 2006). MAPSE found to be useful in the assessment of long-axis myocardial function and a good indicator of LV systolic function (Emilsson K et al., 2000 and Qin et al., 2004) as it correlates with EF (Florian et al., 2012). It was also found that MAPSE is a simple and a sensitive marker for impaired longitudinal function. It may be the earliest marker of myocardial dysfunction in patients having cardiomyopathies with preserved ejection fraction (Florian et al., 2012) in whom MAPSE observed to be abnormally low compared

with the normal population (Elnoamany et al., 2006). In our study, we found that MAPSE increased significantly in the whole group as well as responders (4.8% and 5.7% respectively) 6 months after RD as a therapy for resistant HTN. Improvement of MAPSE after therapy may denote early recovery of long-axis myocardial function, which is suspected the first to be lost as part of LVH pathology, and this recovery associated also the regression of LV mass index and Doppler diastolic parameters in the same studied population. This improvement may be also preceding the recovery of the whole LV systolic function represented by EF which did not show significant increase in our study, compared with Berndt et al 2012. We supposed that, especially this increase in MAPSE correlated positively with changes in EF as well as the improvement of systolic strain parameters (see later) in our patients after RD.

On the other hand, the non responders did not show an observed significant improvement in MAPSE despite the regression of LV mass index. These observations came in association also with failure of the Doppler diastolic parameters to recover in the mentioned sub group.

8.2.5. Impact of RD on 2D echocardiography SRI parameters

8.2.5.1. Impact of RD on diastolic SRI parameters

Assessment of diastolic dysfunction complicating systemic hypertension is frequently encountered in daily clinical practice. There is an emerging role for SRI in the assessment of DD as it provides new physiologic and pathophysiologic information. Early strain rate parameter (SRE) is shown to be useful for detecting abnormalities in early diastolic phase (Støylen et al., 2001). Global SRE reflects LV relaxation, LV stiffness and is influenced by preload conditions (Park et al, 2004 and Pislaru et al., 2004). Similar to E′, SRE is influenced by late systolic recoil and arterial load (Borlaug et al., 2007, Wang et al 2007, Pavlopoulos et al., 2008 and Wang et al 2008 a). Some researchers are convinced that SRE was the most informative parameter in the assessment of hypertensive hypertrophic subjects, especially in those having concentric hypertrophy pattern of LVH (Kim et al., 2008). Reduction of global SRE was associated with global DD (Pislaru et al., 2004 and

Park et al, 2006) as both peak strain rate and propagation of stretching are reduced in diastolic dysfunction (Støylen et al., 2001).

The ratio of E and SRE (E/SRE) was observed to be significantly related to LV filling pressure and might predict it (Goto et al., 2006, Dokainish et al., 2008. and Kasner et al., 2010). Recently, E/SRE ratio was introduced as analogous to the LV filling index parameter, E/E′ (Wang J, et al., 2007).

In our study, SRE did not show significant change in the whole patients after RD as well as the subgroups. As SRE reflects LV relaxation and stiffness, we subdivided the patients according to the existence of DD at the baseline, according to the novel standard parameters. We observed that those who had evidence of DD at baseline showed improvement in SRE 6 months after the procedure. That came in parallel with the significant improvement of the conventional diastolic parameters derived from Doppler and TDI in the same subgroup. This was not observed in the others who had no evidence of DD at baseline. That confirms that SRE is influenced mainly by LV relaxation. 37 (54.4%) patients from our population had impaired relaxation at base line decreased to be only 19 (27.9%) patients who had impaired relaxation at the end of follow-up period. Improvement of SRE was also found to be positively correlated with improvement of E max, E/A ratio, E' sep. and E' lat. On the other hand, it was negatively correlated with decrease in LVEDD which supports that the improvement of diastolic parameters is linked to change of LV geometry and LV systolic function (see later). E/SRE ratio did not show statistically significant improvement in the all the involved subgroups, however, the changes in E/SRE ratio was found to be positively correlated with both E/E' and E/E' lat. ratios and that is corresponding to Wang et al observations (Wang J, et al., 2008 b).

In contrast to the SRE, strain rate during the late diastolic filling (SRL) was not observed to show significant improvement, also in the subgroup of patients who had DD at baseline. This was unexpected since it was demonstrated that the strain rate pattern after the early lengthening wave depends mainly on LV passive recoil processes in late diastole. Impairment of early diastolic filling is usually compensated by the augmentation of LV filling during atrial systole incrementing the late ventricular lengthening (Kasner et al., 2010). Kasnerl et al 2010 found that late diastolic filling was related neither to LV

relaxation nor compliance parameters obtained from pressure-volume loop analysis when they estimated the diastolic function in HFpEF by SRI compared with pressure–volume loop analysis. They owed that to mild impairment of left atrial function and thus no abnormalities were found in the late diastolic lengthening in their population.
In contrast to SRI, the TDI measurements are still quicker and may be more convenient for daily practice for evaluation of diastolic function of LV, whereas SRI data needs deeper insight but enables more detailed analysis of diastolic pathophysiology. It was helpful in better understanding the changes in the early diastolic phase, as well as systolic phase (see later), of the LV that occurred in concomitant with LV mass regression after RD therapy. Concomitant invasive manoeuvre for the analysis of pressure-volume loops during diastole in our population is recommended to support these findings and to understand myocardial pathomechanisms in late diastole.

8.2.5.2. Impact of RD on systolic SRI parameters

The conventional echocardiography is considered to be reliable for ventricular wall motion analysis and assessment of regional myocardial function, but the visual estimation of wall motion is still very subjective and highly operator dependent. It also has high interobserver and intraobserver variability with limited evaluation of radial displacement and deformation, without the possibility of assessing myocardial shortening (Sheehan et al., 2002 and Perk et al., 2007). During recent years, velocity imaging, displacement and deformation imaging (strain and strain-rate imaging) have emerged as valuable tools for more detailed and reliable echocardiographic assessment of myocardial function (Perk et al., 2007 and Yu et al., 2007).

Systemic arterial hypertension leads to LV macro and microvascular abnormalities beside interstitial myocardial fibrosis. The endocardium is the most vulnerable part to the harmful effects of interstitial fibrosis and hypoperfusion (Martinez et al., 2003). The longitudinal function abnormalities can be early detected by examining subendocardial function, using global longitudinal strain measurement (Wang et al., 2008 a). Application of SRI using Speckle tracking has been used in detecting subclinical myocardial changes

in LV hypertrophy, as well as in distinguishing the different causes of LV hypertrophy (Pavlopoulos et al., 2008 and Imbalzano et al., 2011). Global longitudinal systolic strain and strain rate can also reflect diastolic function of LV. It is proved that impaired global diastolic filling, with a preserved ejection fraction (EF $\geq$ 50%) is associated with longitudinal systolic dysfunction (Vinereanu et al 2005 b). It is found also that longitudinal systolic function estimated by mean strain and SR decreased in the hypertensive group but further deteriorated in the diastolic dysfunction group, compared with control (Pavlopoulos et al., 2008). As we know, the myocardial lengthening is associated with the onset of mitral inflow into the LV (Perry et al., 2008); this may suggest that changes in global longitudinal strain rate may be early markers for disturbances of global diastolic function. Accordingly, measuring of global longitudinal systolic 2D strain appears to be even more important, In agreement with Wang et al (Wang J, et al., 2007).

We aimed in the present study to investigate the effect of RD on GSL and GSR. We studied whether the regression of LVMI is associated with improvement of the global longitudinal strain and hence the myocardial longitudinal systolic function of LV after treatment of resistant hypertension using RD and if that reflecting on the diastolic function of LV. We observed that the GSL increased (improved) in the whole group as well as the responders (6.6% and 7.1% respectively). Changes are the same in non-responders, albeit not significant probably because of the lower number. On the other hand, the involved patients did not show significant change concerning GSR after RD. Interestingly; the improvement in GSL was negatively correlated with LVMI and was positively correlated with MAPSE, which considered also another parameter to evaluate longitudinal systolic function of LV. That confirms a relevant improving in subendocardial function and hence the longitudinal systolic function of LV secondary to regression of LVMI after RD therapy. There were no available reports, according to our knowledge, describing the effect of antihypertensive therapy on longitudinal LV systolic functions in hypertensive patients using SRI. A recent study investigated whether strain, and strain rate could be useful to detect subtle left ventricular dysfunction in patients with aortic stenosis (in which there is also a pressure overload on LV) and changes in regional myocardial function after aortic valve replacement. The authors concluded that strain and

strain rate parameters seemed to relate to LV function and aortic stenosis severity. They seemed to be more sensitive than tissue velocity and conventional echocardiography in detecting tiny changes in myocardial function after AVR and even before the expected improvement in LV mass and LV function (Iwahashi et al., 2006).

In another study (Becker et al., 2007), the authors tried to recognize the impact of changes in LV loading conditions on myocardial deformation parameters. They revealed that myocardial deformation parameters change significantly immediately after AVR for aortic stenosis or aortic insufficiency indicating a dependency of determined myocardial deformation parameters on LV preload and afterload. By studying the correlation between systolic and diastolic SRI parameters, we found the changes in GSL and GSR both correlated positively with changes SRE and SRL and both correlated negatively with E/SRE ratio in the whole group. That helps in better understanding the myocardial deformation during systolic and diastolic phases and supports the high relation between longitudinal systolic and diastolic dysfunction. It also explains how the improvement in systolic parameters in response to RD as a treatment of resistant hypertension could contribute to the improvement in LV relaxation and stiffness and hence the diastolic function of the LV. Furthermore, it also suggests that subendocardial myocardium performs a functioning compartment and contributes to the whole cardiac performance. This compartment seems to play an important role in development and progression of diastolic dysfunction and diastolic heart failure which is corresponded to some recent studies (Brutsaert et al., 2006 and Pavlopoulos et al., 2008).

9. Limitations of the Study

No control group in this prospective 6-month study. Control group with placebo, which would be the ideal control, is probably over the ethical standpoint for such a long period. The coexistence of coronary artery disease has not been excluded in all the hypertensive patients; however, there was no evidence for coronary artery disease from ECG or chest pain on exertion. Independent confirmation of global DD using invasive hemodynamic measurements was not performed. Still a major limitation using echocardiographic speckle tracking is its dependence on high-quality images. Adequate speckles in the echocardiographic image for speckle tracking to track in each frame are important for it to work optimally. Reduction in image quality (e.g. poor quality parasternal window and significant lung disease) significantly affecting the ability of the software to process the data.

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11. PUPLICATIONS

- Thesis for partial fulfilment for the Master degree in Cardiology from Assiut University under the title of "**Links between Cardiovascular Risks and Hormonal Contraception in Women**". In 2007.
- Marwa A. Sayed, SH Schirmer, F. Mahfoud, M. Böhm. Diastolic strain parameters improve in resistant hypertensive patients treated with renal sympathetic denervation. (Abstract-oral presentation). ESC Congress, Munich, August 2012.

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